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PREDICTING RESPONSE TO
ANTI-ANGIOGENIC DRUGS AND
PROGNOSIS OF CANCER**(30) **Foreign Application Priority Data**

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2600/158 (2013.01)

(57)

ABSTRACT(21) Appl. No.: **15/116,641**(22) PCT Filed: **Feb. 9, 2015**(86) PCT No.: **PCT/GB2015/050352**

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7, 2014.

Methods for selecting whether to administer an anti-angiogenic therapeutic agent to a subject include steps of measuring the expression levels of one or more biomarkers selected from Table 2 or Table 3 in a sample from the subject; assessing from the expression levels of the one or more biomarkers whether the sample from the subject is positive or negative for a biomarker signature, wherein if the sample is positive for the biomarker signature an anti-angiogenic therapeutic agent is contraindicated. Related prognostic methods and treatment methods are also provided. The invention is particularly applicable in ovarian and colorectal cancers.

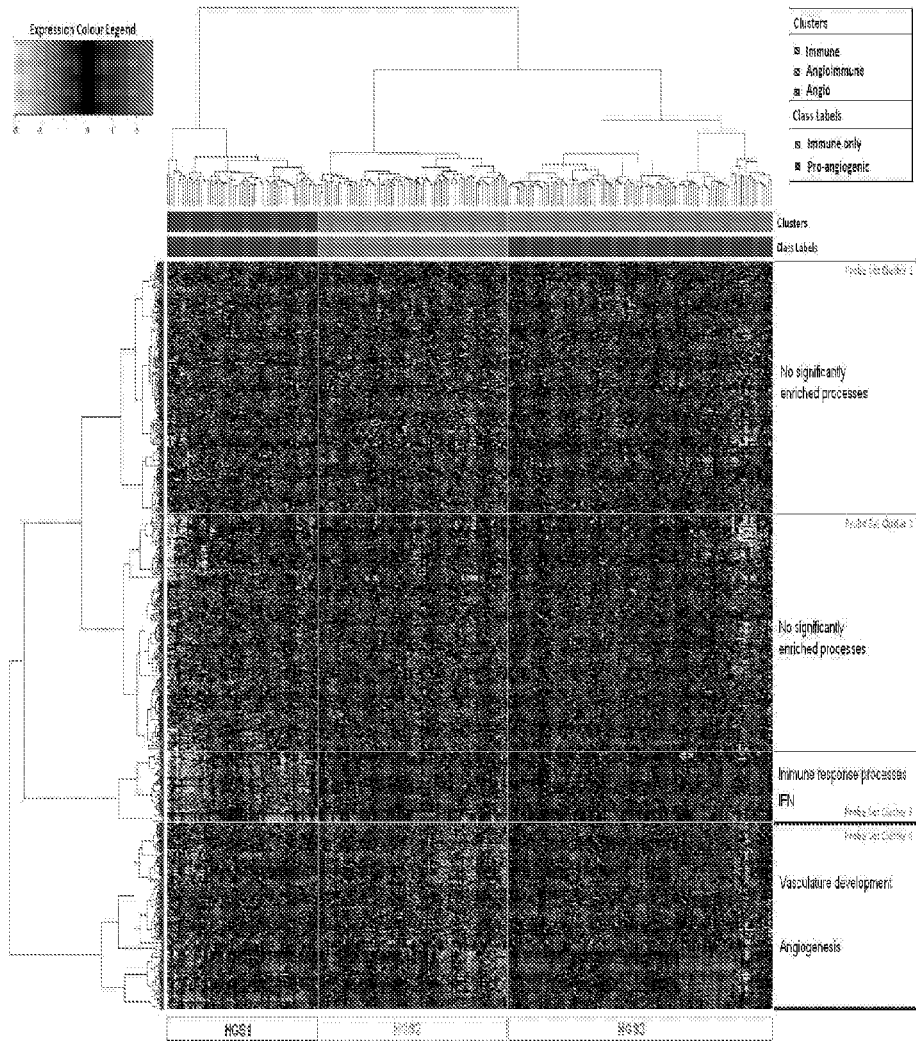


Figure 1

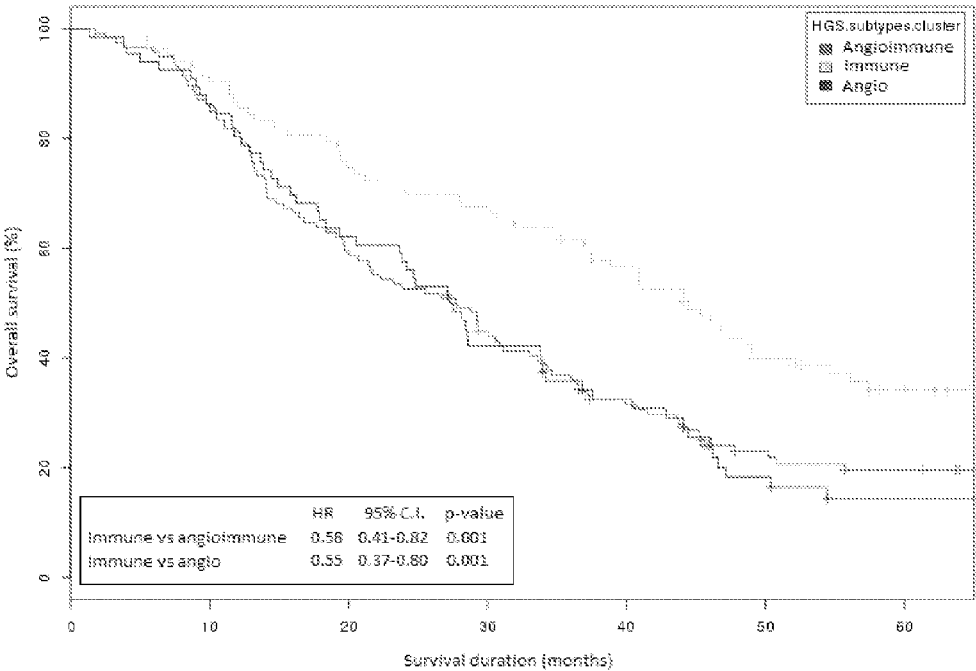
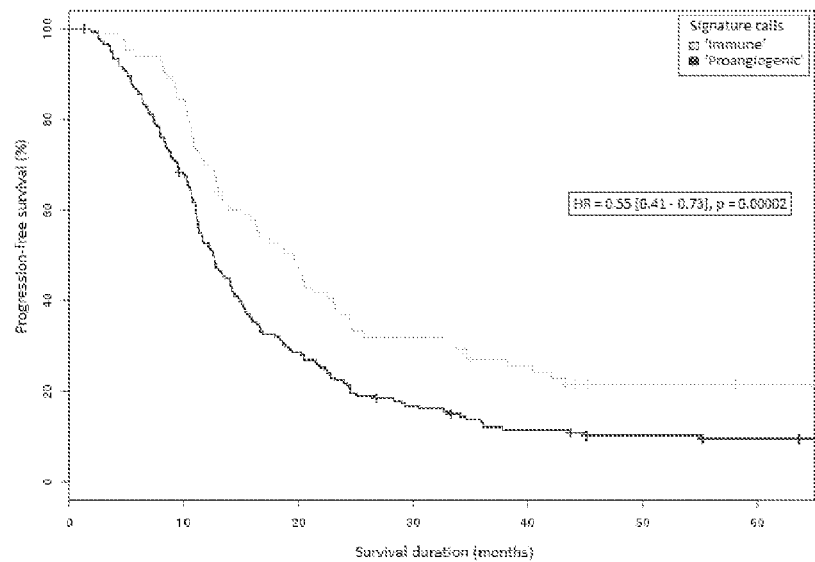


Figure 2

A)



B)

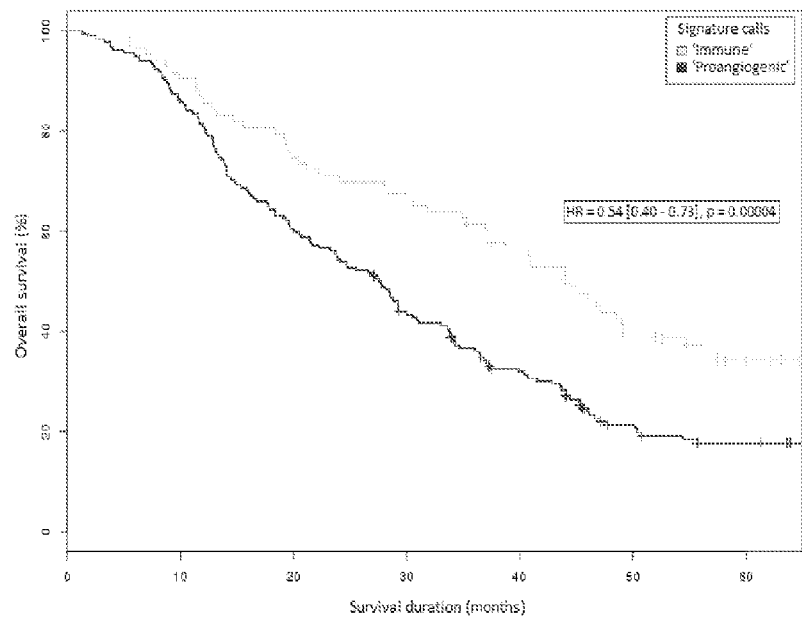


Figure 3

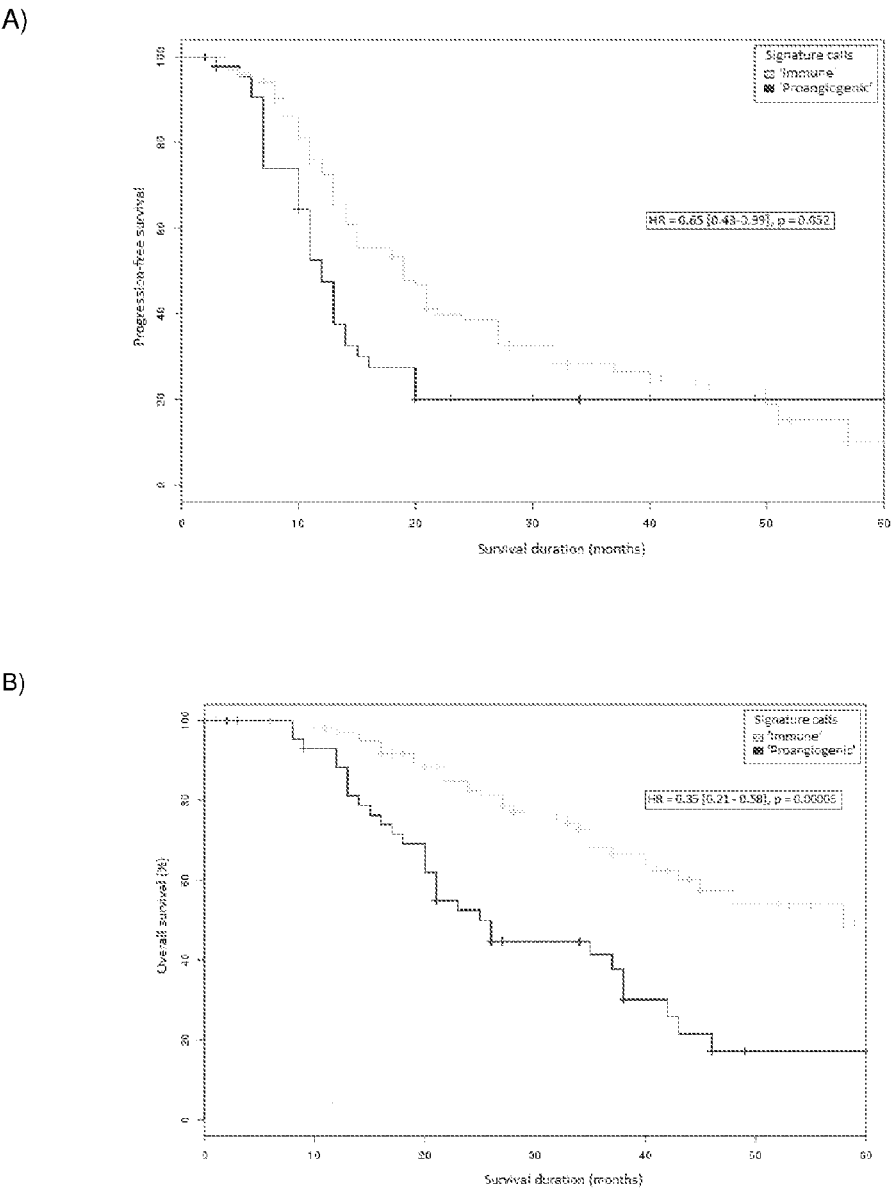
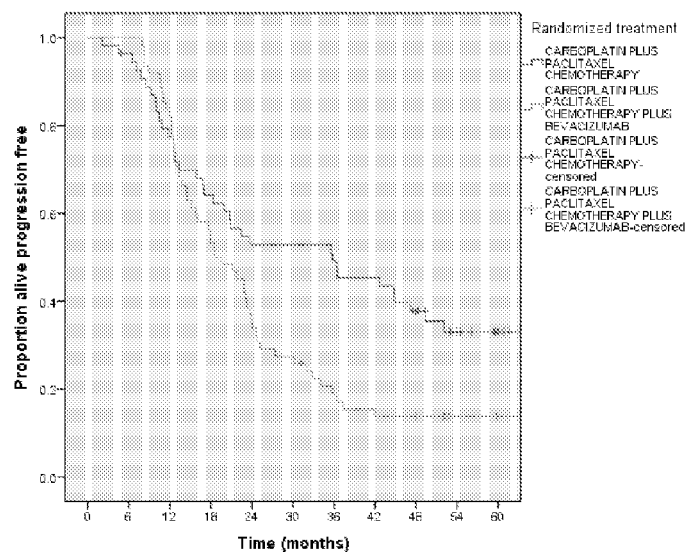


Figure 4

A)



B)

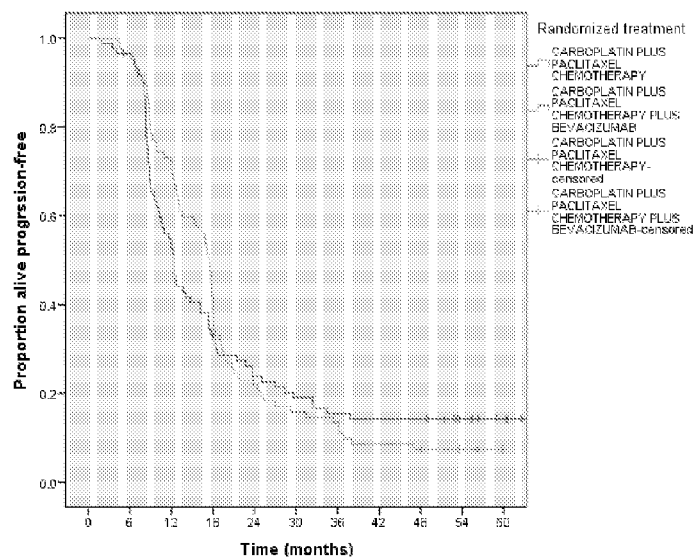
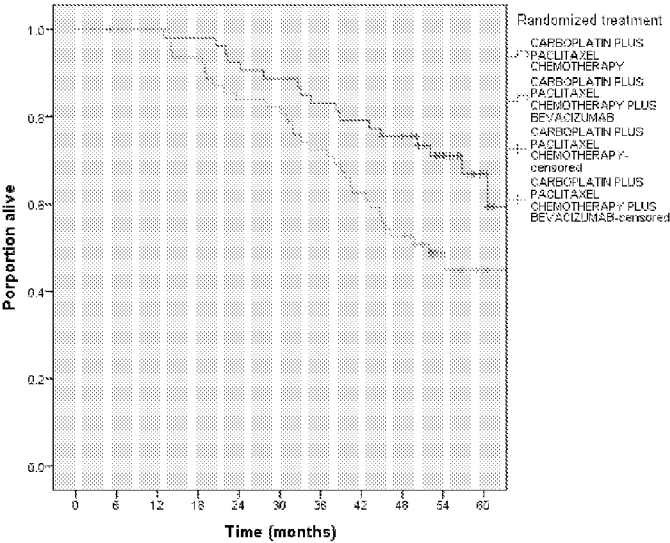


Figure 5

A)



B)

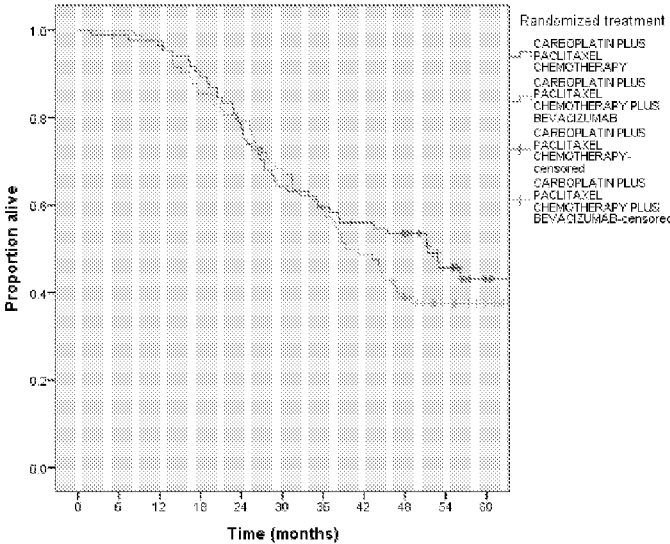


Figure 6

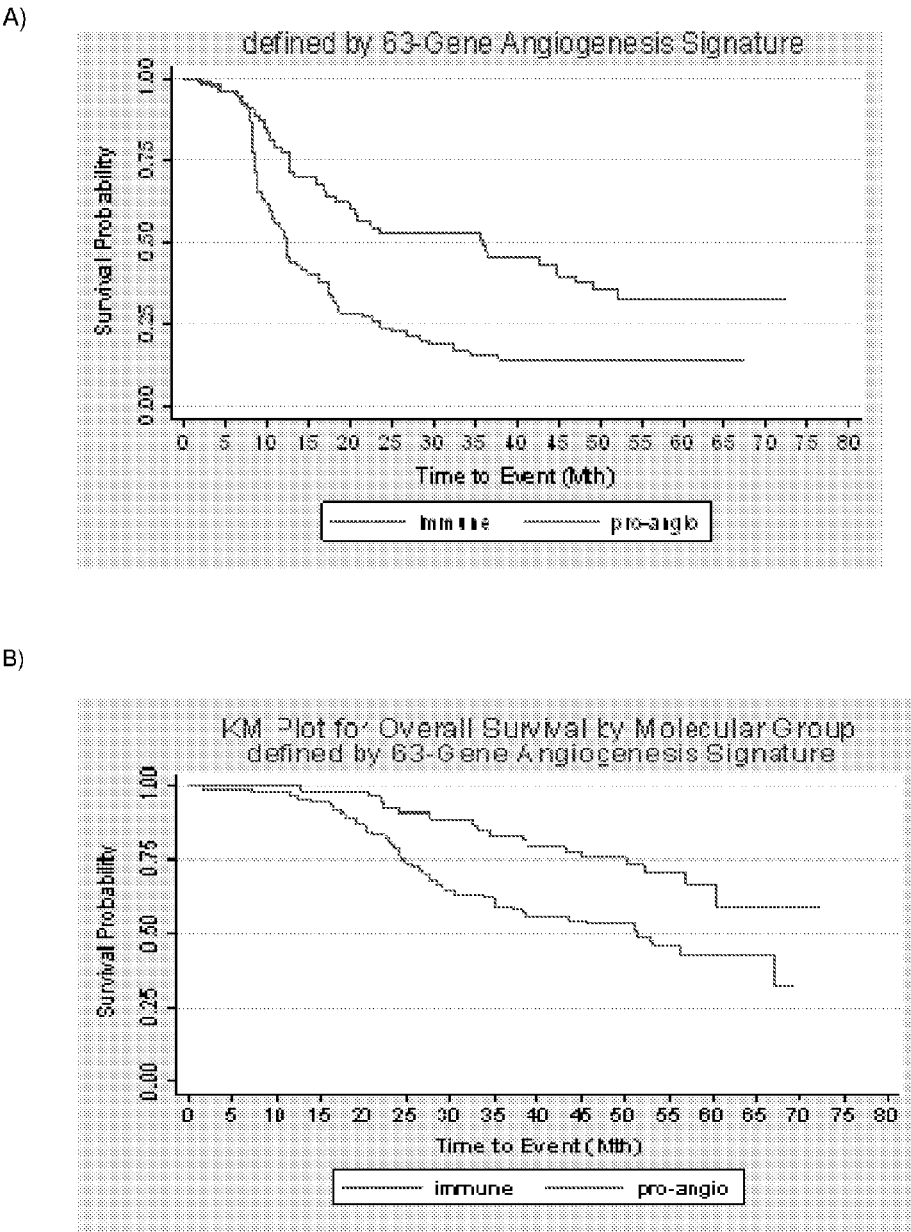


Figure 7

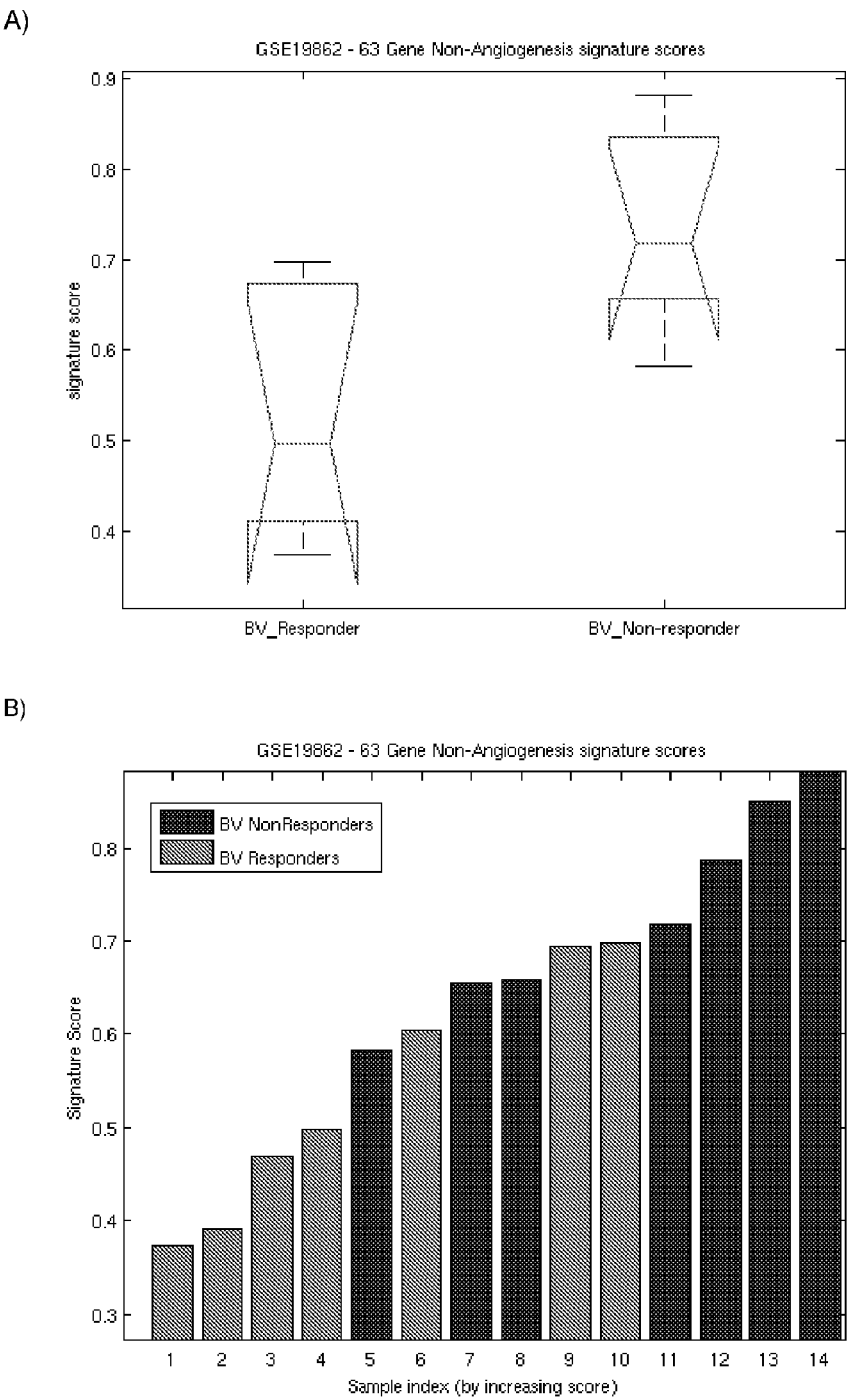


Figure 8

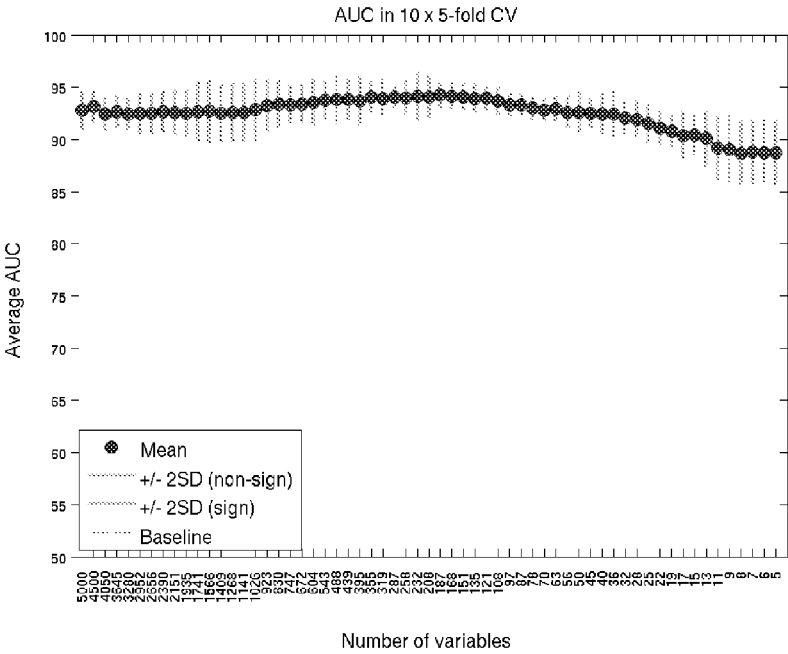


Figure 9

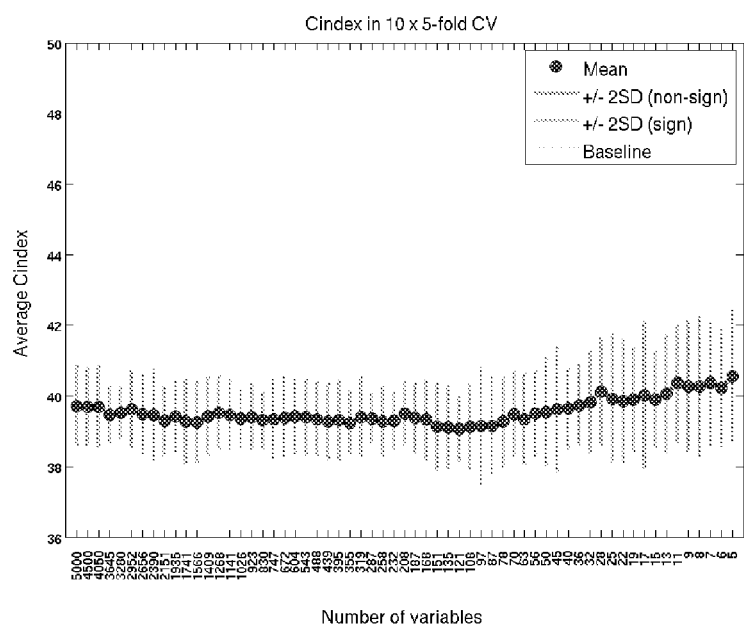


Figure 10

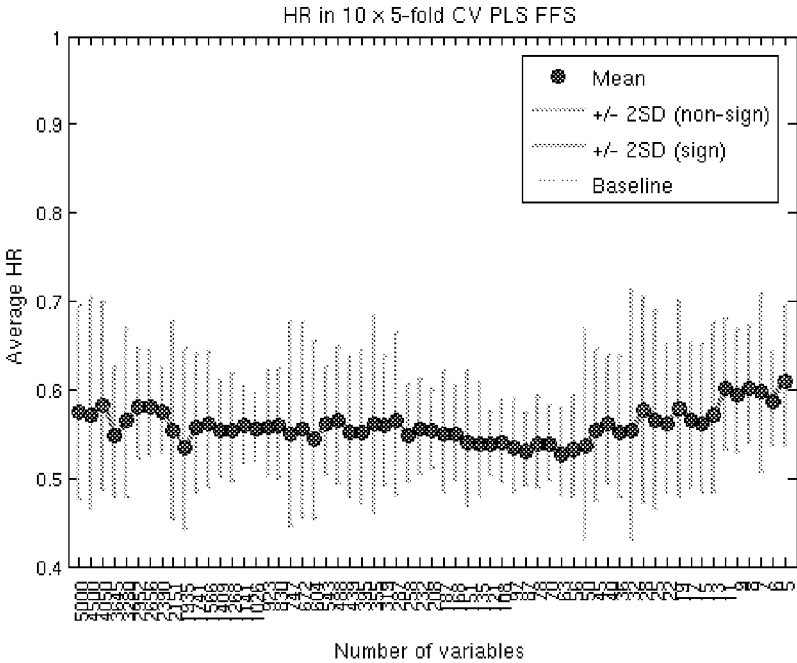


Figure 11

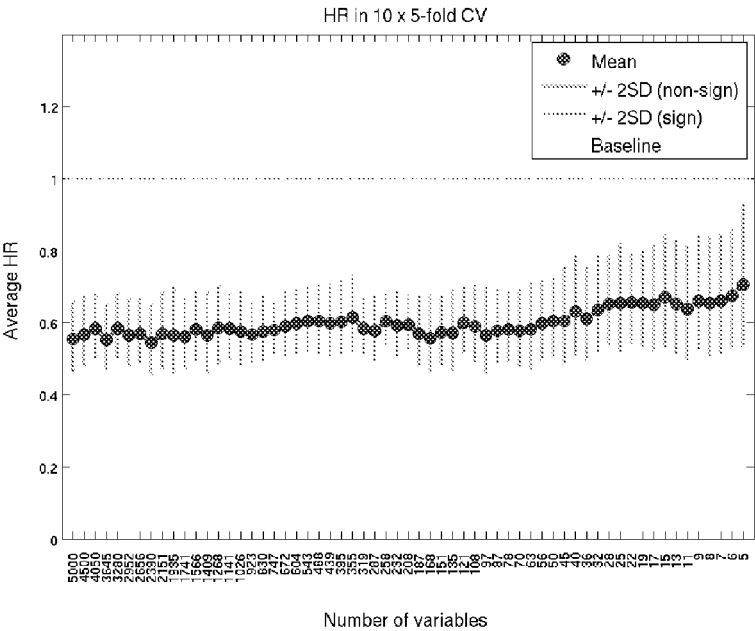


Figure 12

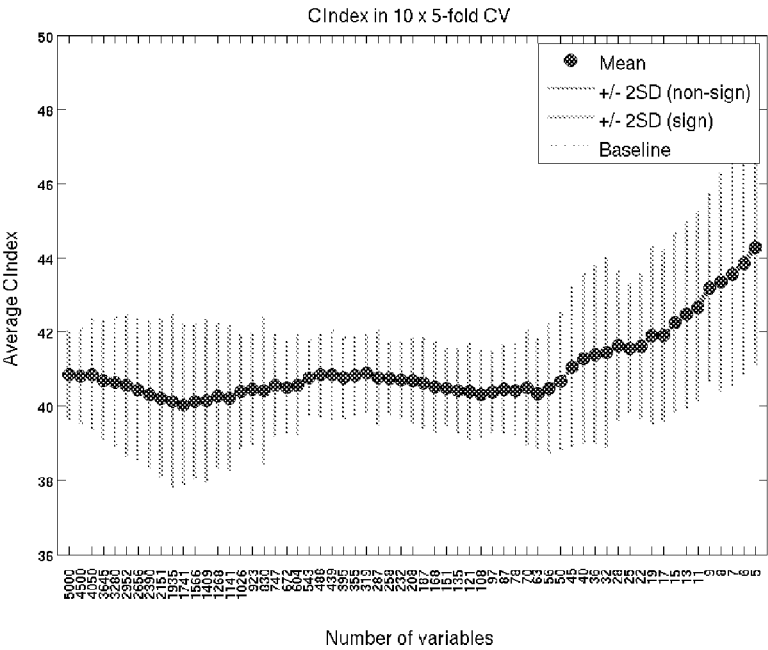


Figure 13

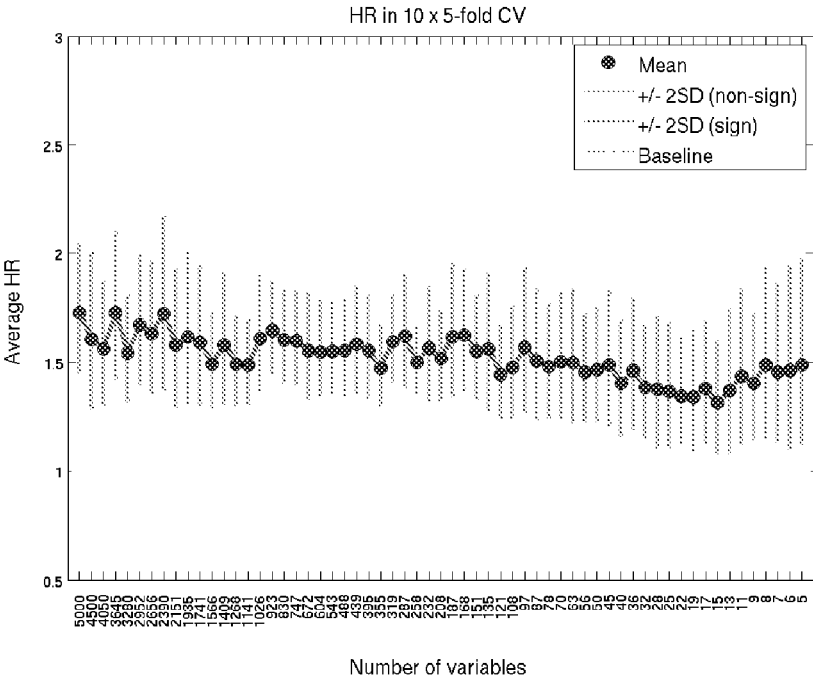


Figure 14

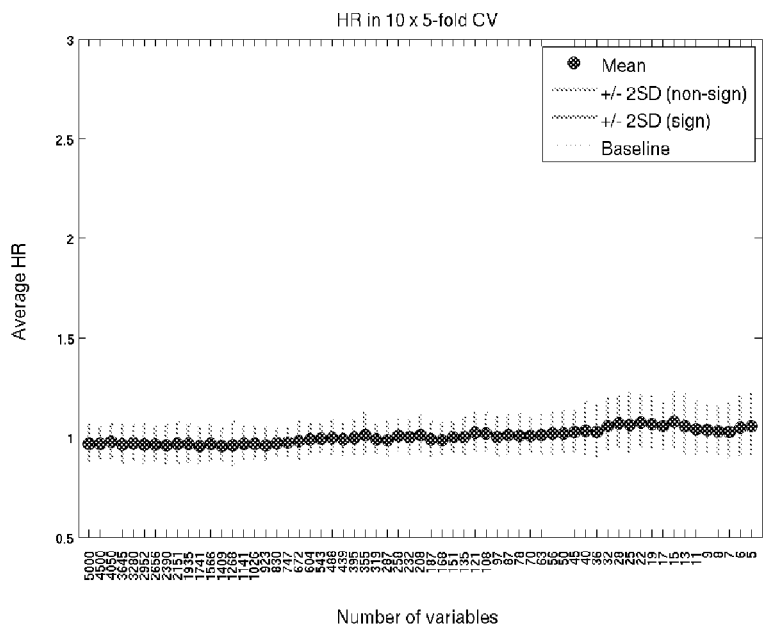


Figure 15

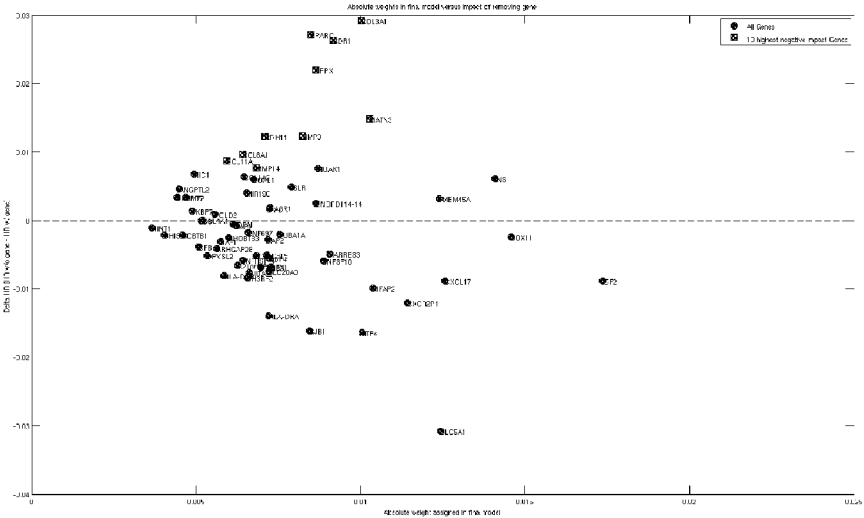


Figure 16

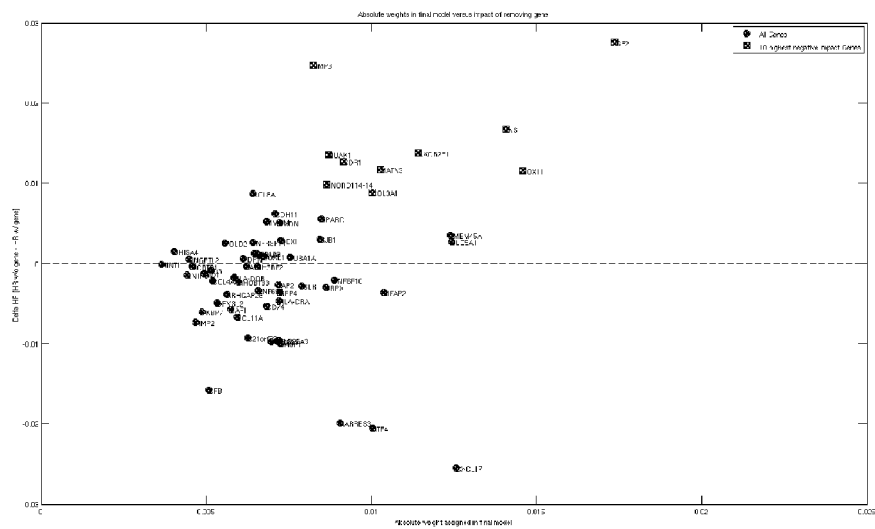


Figure 17

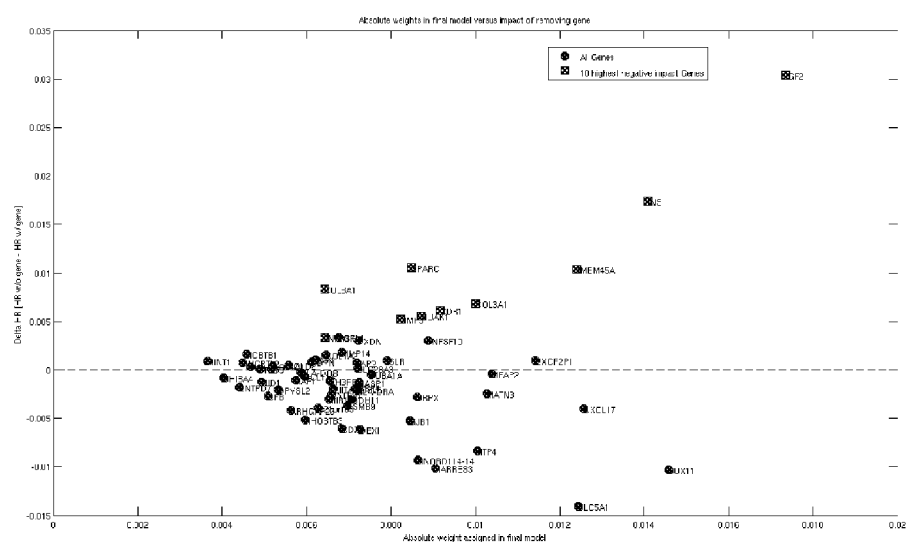


Figure 18

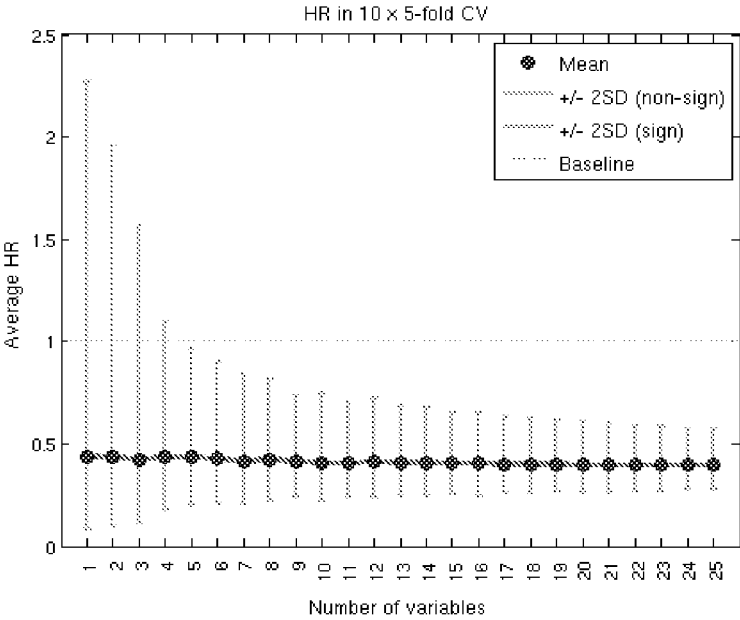


Figure 19

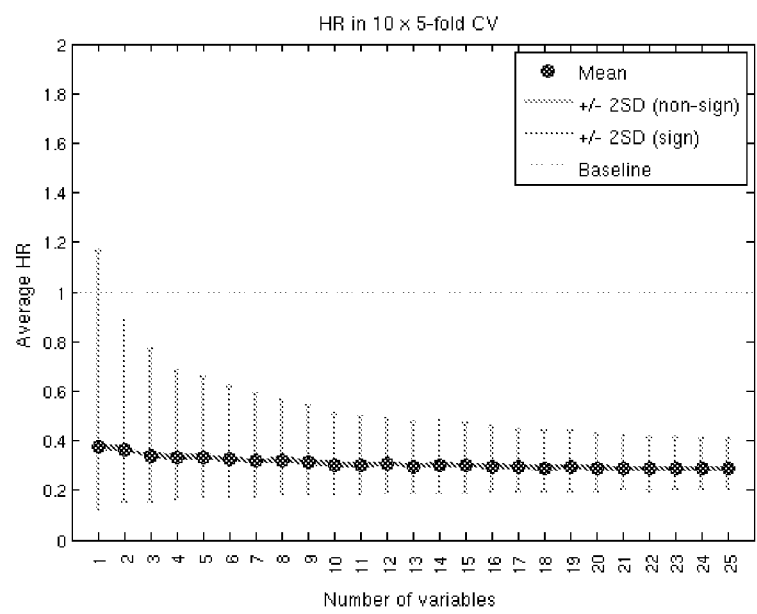


Figure 20

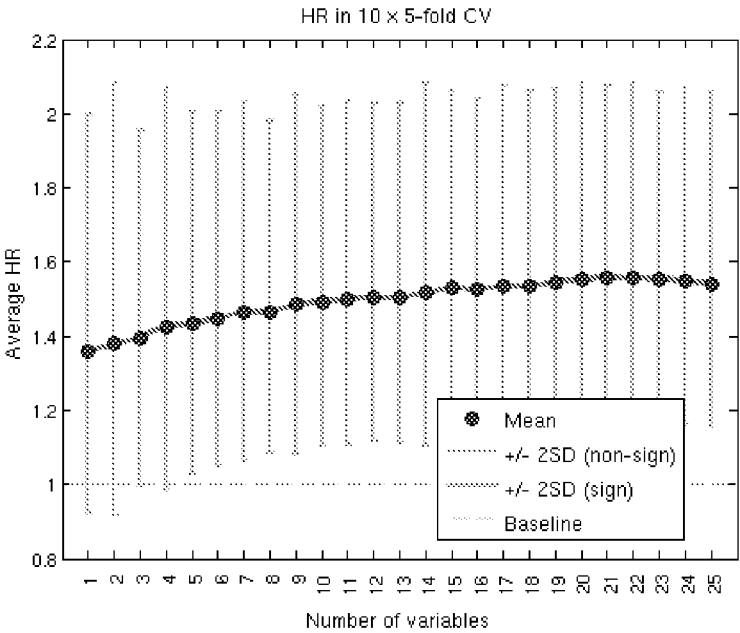


Figure 21

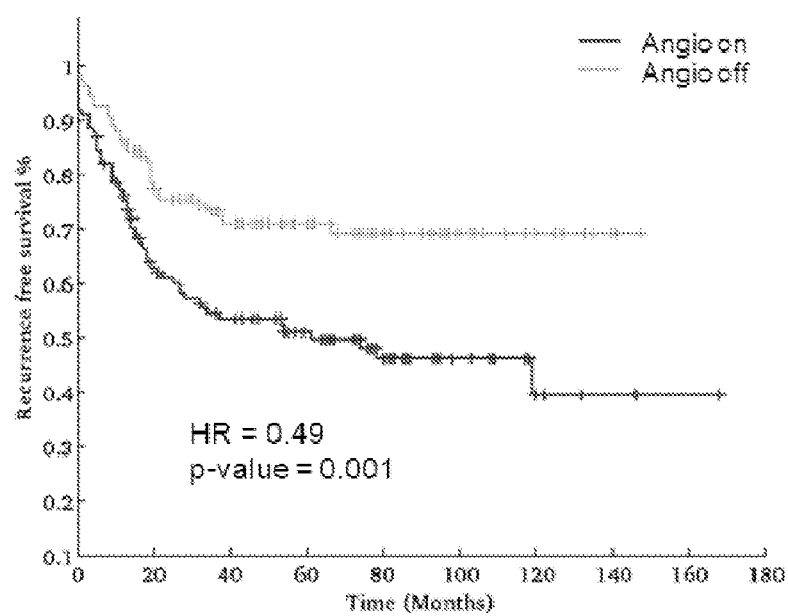


Figure 22

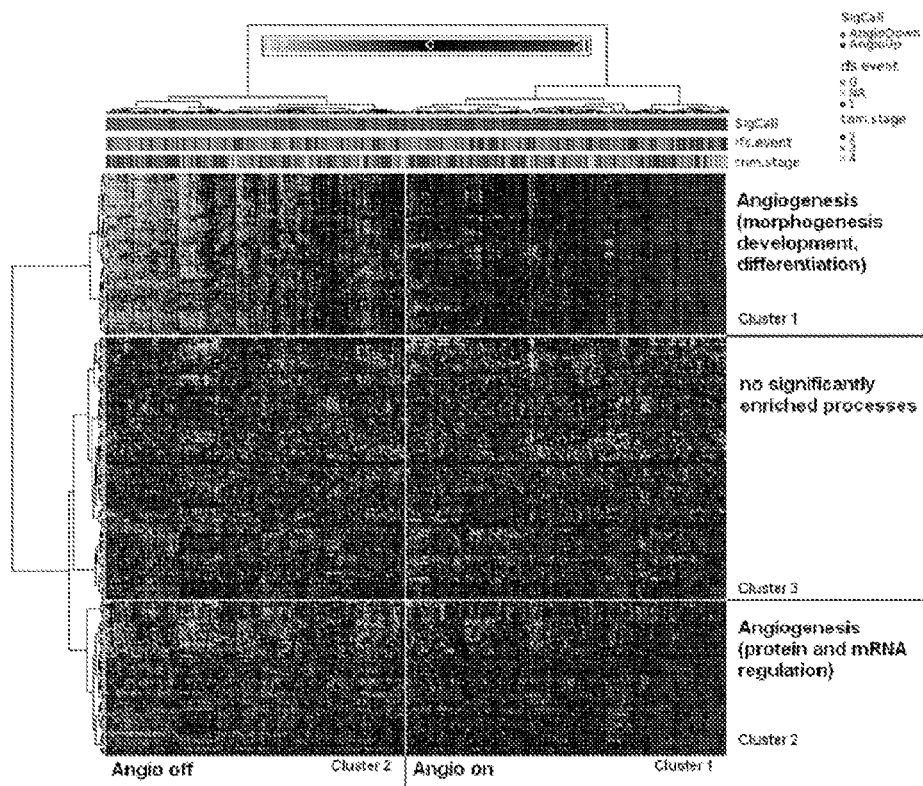
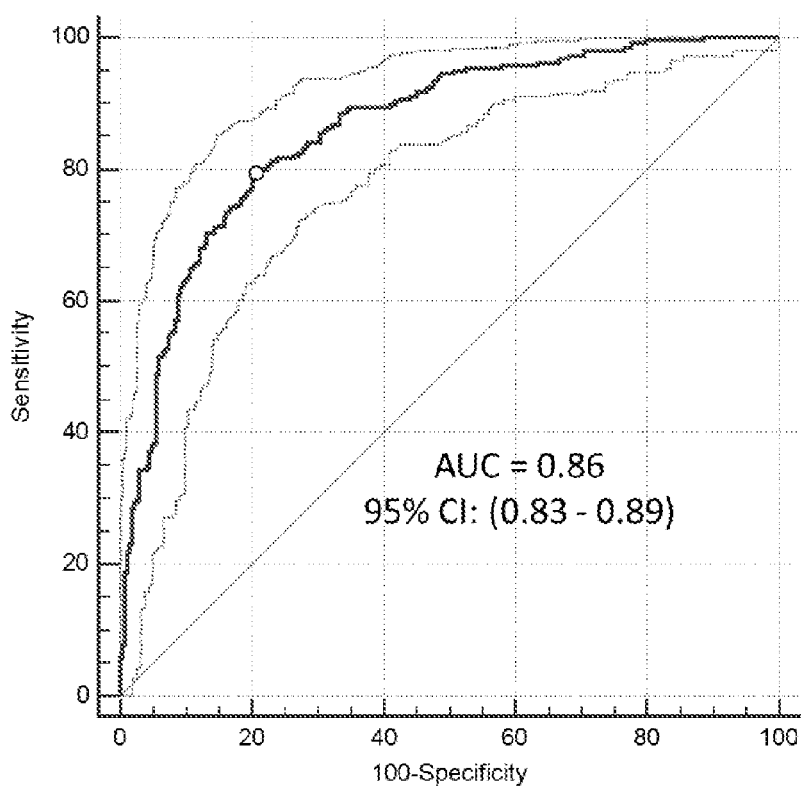


Figure 23

**Figure 24**

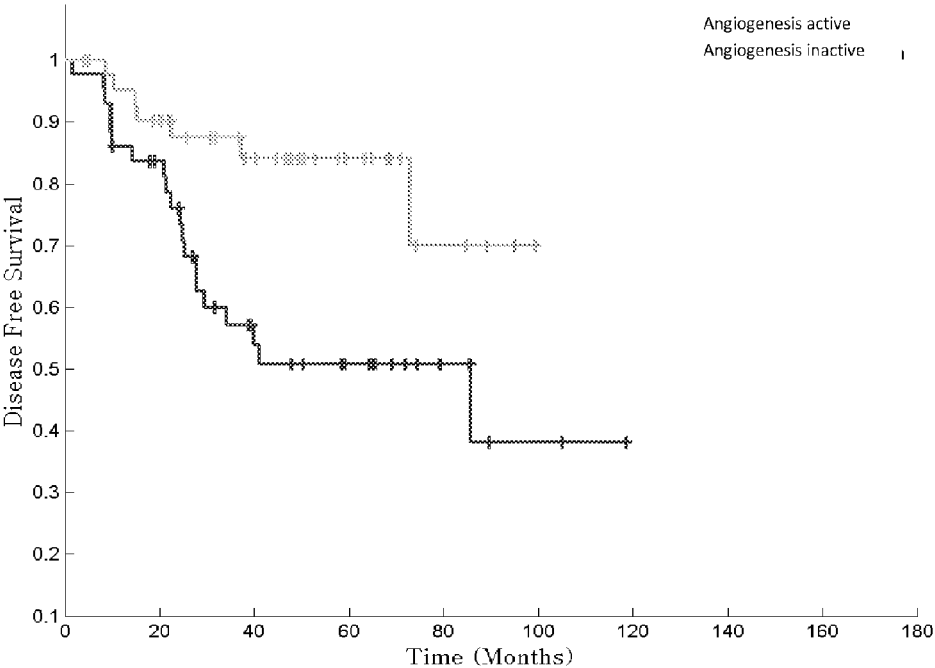


Figure 25

**MOLECULAR DIAGNOSTIC TEST FOR
PREDICTING RESPONSE TO
ANTI-ANGIOGENIC DRUGS AND
PROGNOSIS OF CANCER**

FIELD OF THE INVENTION

[0001] The present invention relates to a molecular diagnostic test useful for providing a prognosis and directing treatment of cancers from different anatomical sites. The invention includes the derivation of a gene classification model from gene expression levels. One application is the selection of whether to administer certain therapeutics, such as anti-angiogenic therapeutics, to subjects receiving a standard of care cancer therapy. Another application is the stratification of cancer patients into those that have a good clinical prognosis or poor clinical prognosis. The present invention provides a test that can guide therapy selection as well as selecting patient groups for enrichment strategies during clinical trial evaluation of novel therapeutics. The invention can be used as a prognostic indicator for certain cancers including ovarian cancer, breast cancer, colon, prostate, lung and glioblastoma. The angiogenesis subtype can be identified from fresh/frozen (FF) or formalin fixed paraffin embedded FFPE patient samples.

BACKGROUND

[0002] The pharmaceutical industry continuously pursues new drug treatment options that are more effective, more specific or have fewer adverse side effects than currently administered drugs. Drug therapy alternatives are constantly being developed because genetic variability within the human population results in substantial differences in the effectiveness of many established drugs. Therefore, although a wide variety of drug therapy options are currently available, more therapies are always needed in the event that a patient fails to respond.

[0003] Traditionally, the treatment paradigm used by physicians has been to prescribe a first-line drug therapy that results in the highest success rate possible for treating a disease. Alternative drug therapies are then prescribed if the first is ineffective. This paradigm is clearly not the best treatment method for certain diseases. For example, in diseases such as cancer, the first treatment is often the most important and offers the best opportunity for successful therapy, so there exists a heightened need to choose an initial drug that will be the most effective against that particular patient's disease.

[0004] Ovarian cancer is the leading cause of death among all gynecological cancers in western countries. This high death rate is due to the diagnosis at an advanced stage in most patients. Epithelial ovarian cancer (EOC) constitutes 90% of ovarian malignancies and is classified into distinct histologic categories including serous, mucinous, endometrioid, clear cell, transitional, mixed, and undifferentiated subtypes. There is increasing evidence that these differed histologies arise from different aetiologies. There have been recent advances in the methodology used to classify epithelial ovarian cancer (McCluggage, W. G. "Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis," *PATHOLOGY* 2011 August; 43(5):420-32). One of the consequences of this is that many tumors that would previously been classified as endometrioid are now being classified as serous.

[0005] The current standard treatment for ovarian cancer is debulking surgery and standard platinum taxane based cytotoxic chemotherapy. However, not all patients respond to this, and of those that do, approximately 70% will experience a recurrence. Specific targeted therapies for ovarian cancer based on histological or molecular classification have not yet reached the marketplace. Similarly for other types of cancer, there is still no accurate way of selecting appropriate cytotoxic chemotherapeutic agents.

[0006] The advent of microarrays and molecular genomics has the potential for a significant impact on the diagnostic capability and prognostic classification of disease, which may aid in the prediction of the response of an individual patient to a defined therapeutic regimen. Microarrays provide for the analysis of large amounts of genetic information, thereby providing a genetic fingerprint of an individual. There is much enthusiasm that this technology will ultimately provide the necessary tools for custom-made drug treatment regimens.

[0007] Currently, healthcare professionals have few mechanisms to help them identify cancer patients who will benefit from chemotherapeutic agents. Identification of the optimal first-line drug has been difficult because methods are not available for accurately predicting which drug treatment would be the most effective for a particular cancer's physiology. This deficiency results in relatively poor single agent response rates and increased cancer morbidity and death. Furthermore, patients often needlessly undergo ineffective, toxic drug therapy.

[0008] Angiogenesis is a key component of neo-vascularisation of tumors and essential to tumorigenesis and metastasis. As such, it is a key area for therapeutic intervention and has been correlated to poor prognosis and reduced survival. This has promoted the development of a number of agents that target angiogenesis related processes and pathways, including the market leader and first FDA-approved anti-angiogenic, bevacizumab (Avastin), produced by Genentech/Roche.

[0009] Treatment regimens that include bevacizumab have demonstrated broad clinical activity¹⁻¹⁰. However, no overall survival (OS) benefit has been shown after the addition of bevacizumab to cytotoxic chemotherapy in most cancers^{8, 12-13}. This suggests that a substantial proportion of tumours are either initially resistant or quickly develop resistance to VEGF blockade (the mechanism of action of bevacizumab). In fact, 21% of ovarian, 10% of renal and 33% of rectal cancer patients show partial regression when receiving bevacizumab monotherapy, suggesting that bevacizumab may be active in small subgroups of patients, but that such incremental benefits do not reach significance in unselected patients.¹⁵⁻¹⁸ As such, the use of a biomarker of response to bevacizumab would improve assessment of treatment outcomes and thus enable the identification of patient subgroups that would receive the most clinical benefit from bevacizumab treatment. This would be particularly relevant in the case of metastatic breast cancer, where the absence of a clinically beneficial biomarker has undermined the use of bevacizumab. Thus far, no such biomarker has been clinically validated to predict bevacizumab efficacy. Hypertension and VEGF polymorphisms are so far the only biomarkers to show potential, but important questions remain about their use in a clinical setting.

[0010] Another approach to anti-angiogenic therapy is simultaneous targeting of multiple angiogenic pathways

rather than selective targeting of the VEGF pathway. Theoretically, multitargeted anti-angiogenic agents should more completely inhibit angiogenesis than agents such as bevacizumab and thus may produce greater therapeutic benefit. It has been postulated that in some tumors, angiogenesis may require VEGF only in the early stages of disease but is driven by additional angiogenic pathways as the disease progresses. Therefore, by targeting multiple pathways, it may be possible to counteract compensatory escape mechanisms that could lead to resistance to VEGF inhibition.

[0011] As for other types of cancer there is still no accurate way of selecting which patients will or will not respond to standard of care with an anti-angiogenic therapeutic or single agent anti-angiogenic therapy.

[0012] What is therefore needed is a molecular diagnostic test that would facilitate the stratification of patients based upon their predicted response to anti-angiogenic therapeutics, either in combination with standard of care or as a single-agent therapeutic. This would allow for the rapid identification of those patients who should receive alternative therapies. Such a molecular diagnostic test should be predictive of therapeutic responsiveness across different cancer types with sufficient accuracy.

SUMMARY OF THE INVENTION

[0013] Disclosed are methods of using one or more biomarkers, or a collection of biomarkers expressed in cancer that identify a subtype of cancer that is associated with an up-regulation in molecular signaling related to immune response and a down-regulation in molecular signaling related to angiogenesis and vasculature development, referred to herein as a “non-angiogenesis” or “immune” subtype. The collection of biomarkers may be defined by an expression signature, and the expression signature is used to assign a cumulative score to the measured expression values of the collection of biomarkers. In different aspects, the biomarkers and expression signatures may form the basis of a single parameter or multiparametric predictive test that could be delivered using methods known in the art such as microarray, next generation sequencing (NGS), Q-PCR, immunohistochemistry, ELISA or other technologies that can quantify mRNA or protein expression.

[0014] In addition, the cancer subtypes described herein are common to many types of cancer and are not limited to a single cancer disease type. Accordingly, the expression signatures of the present invention are not limited to a single cancer type. In certain example embodiments, the non-angiogenesis expression signature comprises two or more biomarkers selected from the biomarkers listed in Tables 1. In another example embodiment, the non-angiogenesis expression signature comprises two or more biomarkers listed in Table 2 or 3. In certain other example embodiments, the expression signature comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2PA, MFAP2, MATN3, or RTP4. In another example embodiment, the expression signature comprises one or more of IGF2, CDR1, COL3A1, SPARC, TIMP3, INS, COL8A1, NUAK1, MATN3, and TMEM45A. In another example embodiment, the expression signature comprises one or more of INS, SPARC, COL8A1, COL3A1, CDR1, NUAK1, TIMP3, and MMP14. In another example embodiment, the non-angiogenesis signature comprises the biomarkers listed in Table 2 and their corresponding weights as determined using a PLS classifier. In another example embodiment, the

non-angiogenesis signature comprises the biomarkers listed in Table 3 and their corresponding ranks within a decision function.

[0015] In one aspect the invention provides a method for selecting whether to administer an anti-angiogenic therapeutic agent to a subject, comprising: measuring the expression level(s) of one or more biomarkers selected from Table 2 or Table 3 in a sample from the subject; assessing from the expression level(s) of the one or more biomarkers whether the sample from the subject is positive or negative for a biomarker signature, wherein if the sample is positive for the biomarker signature an anti-angiogenic therapeutic agent is contraindicated. In certain embodiments assessing whether the sample is positive or negative for the biomarker signature comprises: determining a sample expression score for the one or more biomarkers; comparing the sample expression score to a threshold score; and determining whether the sample expression score is above or equal to the threshold expression score, wherein if the sample expression score is above or equal to the threshold score the sample is positive for the biomarker signature. In further embodiments the subject is receiving or has received treatment with a chemotherapeutic agent.

[0016] In a further aspect the invention provides a method of treating cancer comprising administering a chemotherapeutic agent and not administering an anti-angiogenic therapeutic agent to a subject wherein the subject is selected for treatment on the basis of a method as described herein and the subject is positive for the biomarker signature. According to a further aspect of the invention there is provided a method of treating cancer comprising administering a chemotherapeutic agent and not administering an anti-angiogenic therapeutic agent to a subject wherein the subject is selected for treatment by measuring the expression level(s) of one or more biomarkers selected from Table 2 or Table 3 in a sample from the subject; assessing from the expression levels of the biomarkers whether the sample from the subject is positive or negative for a biomarker signature, wherein if the sample is positive for the biomarker signature the subject is selected for treatment. In yet a further aspect, the present invention relates to a chemotherapeutic agent for use in treating cancer in a subject wherein the subject is selected for treatment on the basis of a method as described herein and is positive for the biomarker signature and wherein the subject is not treated with an anti-angiogenic therapeutic agent. The invention also relates to a chemotherapeutic agent for use in treating cancer in a subject wherein the subject is selected for treatment by measuring the expression level(s) of one or more biomarkers selected from Table 2 or Table 3 in a sample from the subject; assessing from the expression levels of the biomarkers whether the sample from the subject is positive or negative for a biomarker signature, wherein if the sample is positive for the biomarker signature the subject is selected for treatment and wherein the subject is not treated with an anti-angiogenic therapeutic agent. In a further aspect, the present invention relates to a method of treating cancer comprising administering a chemotherapeutic agent to a subject wherein the subject is positive for a biomarker signature defined by the expression levels of one or more biomarkers selected from Table 2 or Table 3 and wherein an anti-angiogenic therapeutic agent is not administered. In yet a further aspect, the present invention relates to a chemotherapeutic agent for use in treating cancer in a subject wherein the subject is positive for a biomarker

signature defined by the expression levels of one or more biomarkers selected from Table 2 or Table 3 and wherein the subject is not treated with an anti-angiogenic therapeutic agent. In certain embodiments the chemotherapeutic agent comprises a platinum-based chemotherapeutic agent, an alkylating agent, an anti-metabolite (such as 5FU), an anti-tumor antibiotic, a topoisomerase inhibitor, a mitotic inhibitor, or a combination thereof. The chemotherapeutic agent may comprise a platinum based-chemotherapeutic agent, a mitotic inhibitor, or a combination thereof. In specific embodiments the chemotherapeutic agent comprises carboplatin and/or paclitaxel. The chemotherapeutic agent may reflect the standard of care treatment for the cancer. The standard of care treatment may differ for different types of cancer—for example carboplatin in ovarian cancer, 5FU in colorectal cancer, platinum in head and neck cancer. According to all aspects of the invention assessing whether the sample is positive or negative for the biomarker signature may comprise determining a sample expression score for the one or more biomarkers; comparing the sample expression score to a threshold score; and determining whether the sample expression score is above or equal to the threshold expression score, wherein if the sample expression score is above or equal to the threshold score the sample is positive for the biomarker signature. According to all aspects of the invention the subject may be suffering from cancer. The cancer may be ovarian cancer, optionally high grade serous ovarian cancer. Herein “administering” an agent is used interchangeably with “treating with” an agent.

[0017] According to a further aspect of the invention there is provided a method for determining clinical prognosis of a subject with cancer, comprising: measuring the expression level(s) of one or more biomarkers selected from Table 2 or Table 3 in a sample from the subject; assessing from the expression level(s) of the one or more biomarkers whether the sample from the subject is positive or negative for a biomarker signature, wherein if the sample is positive for the biomarker signature the subject has a good prognosis. Assessing whether the sample is positive or negative for the biomarker signature may comprise: determining a sample expression score for the biomarkers; comparing the sample expression score to a threshold score; and determining whether the sample expression score is above or equal to the threshold expression score, wherein if the sample expression score is above or equal to the threshold score the sample is positive for the biomarker signature. In certain embodiments the good prognosis indicates increased progression free survival or overall survival rates compared to samples that are negative for the biomarker signature, optionally compared to samples with a sample expression score below the threshold score. In certain embodiments the subject is receiving, has received and/or will receive chemotherapeutic treatment and/or will not receive treatment with an anti-angiogenic therapeutic agent. The chemotherapeutic treatment may comprise administration of a platinum-based chemotherapeutic agent, an alkylating agent, an anti-metabolite, an anti-tumor antibiotic, a topoisomerase inhibitor, a mitotic inhibitor, or a combination thereof. The chemotherapeutic treatment may comprise administration of a platinum-based chemotherapeutic agent, a mitotic inhibitor, or a combination thereof. In specific embodiments the chemotherapeutic treatment comprises administration of paclitaxel and carboplatin. The cancer may be ovarian cancer or colorectal cancer

[0018] In a further aspect the present invention relates to a method for selecting whether to administer Bevacizumab to a subject, comprising: in a test sample obtained from a subject suffering from ovarian cancer, which subject is being, has been and/or will be treated using a platinum-based chemotherapeutic agent and/or a mitotic inhibitor; measuring expression levels of one, two or more, up to all of the, biomarkers selected from Table 2; assessing from the expression level(s) of the one, two or more biomarkers whether the sample from the subject is positive or negative for a biomarker signature, selecting a treatment based on whether the sample is positive for the biomarker signature, wherein if the sample is positive for the biomarker signature Bevacizumab is contraindicated. In certain embodiments assessing whether the sample is positive or negative for the biomarker signature comprises determining a sample expression score for the one, two or more biomarkers; comparing the sample expression score to a threshold score; and determining whether the sample expression score is above or equal to the threshold expression score, wherein if the sample expression score is above or equal to the threshold score the sample is positive for the biomarker signature.

[0019] The invention also relates to a method for determining clinical prognosis of a subject, comprising: (a) in a test sample obtained from a subject suffering from ovarian cancer, which subject is being, has been and/or will be treated using a platinum-based chemotherapeutic agent and/or a mitotic inhibitor; (b) measuring expression levels of one or more, up to all of the, biomarkers selected from Table 2 or Table 3; (c) assessing from the expression level(s) of the one or more biomarkers whether the sample from the subject is positive or negative for a biomarker signature, wherein if the sample is positive for the biomarker signature the subject has a good prognosis. Assessing whether the sample is positive or negative for the biomarker signature may comprise: (i) determining a sample expression score for the one or more biomarkers; (ii) comparing the sample expression score to a threshold score; and (iii) determining whether the sample expression score is above or equal to the threshold expression score, wherein if the sample expression score is above or equal to the threshold score the sample is positive for the biomarker signature. In certain embodiments the good prognosis indicates increased progression free survival or overall survival rates compared to samples that are negative for the biomarker signature, optionally compared to samples with a sample expression score below the threshold score.

[0020] According to all aspects of the invention the expression level(s) of two or more biomarkers selected from Table 2 or Table 3 may be measured in a sample from the subject. The expression level(s) of five or more biomarkers selected from Table 2 or Table 3 may be measured in a sample from the subject. Assessing whether the sample is positive or negative for the biomarker signature may comprise the use of classification trees or random forests. Classification trees (Breiman, Leo; Friedman, J. H.; Olshen, R. A.; Stone, C. J. (1984). Classification and regression trees. Monterey, Calif.: Wadsworth & Brooks/Cole Advanced Books & Software. ISBN 978-0-412-04841-8) provide a means of predicting outcomes based on logic and rules. A classification tree is built through a process called binary recursive partitioning, which is an iterative procedure of splitting the data into partitions/branches. The goal is to build a tree that distinguishes among pre-defined classes.

Each node in the tree corresponds to a variable. To choose the best split at a node, each variable is considered in turn, where every possible split is tried and considered, and the best split is the one which produces the largest decrease in diversity of the classification label within each partition. This is repeated for all variables, and the winner is chosen as the best splitter for that node. The process is continued at the next node and in this manner, a full tree is generated. One of the advantages of classification trees over other supervised learning approaches such as discriminant analysis, is that the variables that are used to build the tree can be either categorical, or numeric, or a mix of both. In this way it is possible to generate a classification tree for predicting outcomes based on say the directionality of gene expression. Random forest algorithms (Breiman, Leo (2001). "Random Forests". *Machine Learning* 45 (1): 5-32. doi:10.1023/A:1010933404324) provide a further extension to classification trees, whereby a collection of classification trees are randomly generated to form a "forest" and an average of the predicted outcomes from each tree is used to make inference with respect to the outcome.

[0021] In one aspect, a method for selecting whether to administer an anti-angiogenic therapeutic agent to a subject using the expression signatures disclosed herein is provided, the method comprising obtaining a test sample from the subject, measuring expression levels of a biomarker panel from the test sample, determining a sample expression score for the biomarker panel, comparing the sample expression score to a threshold score, and selecting a treatment based on whether the expression score is equal to or above the threshold score. In certain example embodiments, a sample expression score is equal to or above the threshold score indicates an anti-angiogenic agent is contraindicated and should not be administered to the subject. In certain example embodiments, a sample expression score below the threshold score indicates an anti-angiogenic agent is not contraindicated and can be administered to the subject. A therapeutic agent is "contraindicated" or "detrimental" to a patient if the cancer's rate of growth is accelerated as a result of contact with the therapeutic agent, compared to its growth in the absence of contact with the therapeutic agent. Growth of a cancer can be measured in a variety of ways. For instance, the size of a tumor, or measuring the expression of tumor markers appropriate for that tumor type. A therapeutic agent can also be considered "contraindicated" or "detrimental" if the patient's overall prognosis (progression free survival and overall survival) is reduced by the administration of the therapeutic agent. In one example embodiment, the expression signature disclosed herein may determine a patient's clinical prognosis upon administration of an anti-angiogenic agent following standard cancer therapy.

[0022] In certain example embodiments, the subject suffers from cancer. The cancer may include, but is not limited to, ovarian cancer, breast cancer, colon cancer, colorectal cancer, glioblastoma, kidney cancer, including renal cell carcinoma, hepatocellular cancer, thyroid cancer, pancreatic cancer, neuroendocrine cancer, esophageal cancer, gastrointestinal stromal tumors (GIST), gastric cancer, liver cancer, including adult primary liver cancer, lymphoma, melanoma, or multiple myeloma. In certain example embodiments, the cancer is ovarian cancer. In certain other example embodiments, the ovarian cancer is high grade serous ovarian cancer. In certain example embodiments, the patient may have received, is receiving and/or will receive a treatment

which may be a standard of care treatment for the cancer type of the subject. In certain example embodiments, that treatment which may be a standard of care treatment may include treatment with a chemotherapeutic agent. The chemotherapeutic treatment may include administration of a platinum-based chemotherapeutic agent, an alkylating agent, an anti-metabolite, an anti-tumor antibiotic, a topoisomerase inhibitor, a mitotic inhibitor, or a combination thereof. In certain example embodiments, the chemotherapeutic treatment comprises administration of a platinum-based chemotherapeutic agent, a mitotic inhibitor, or a combination thereof. In certain other example embodiments, the chemotherapeutic treatment comprises administration of carboplatin and paclitaxel. In one example embodiment, the subject has high grade serous ovarian cancer and has previously received a platinum-based chemotherapeutic agent and a mitotic inhibitor. In another example embodiment, the subject has high grade serous ovarian cancer and has previously received carboplatin and paclitaxel. The anti-angiogenic therapeutic agent may be a VEGF-pathway-targeted therapeutic agent (such as bevacizumab or aflibercept), an angiopoietin-TIE2 pathway inhibitor, an endogenous angiogenic inhibitor, or an immunomodulatory agent. In one example embodiment, the anti-angiogenic therapeutic agent is a VEGF-pathway-targeted therapeutic agent. In another example embodiment, the anti-angiogenic therapeutic agent is bevacizumab.

[0023] In another aspect, a method for determining a clinical prognosis of a subject using the expression signatures disclosed herein is provided, the method comprising obtaining a test sample from the subject, measuring expression levels of a biomarker panel from the test sample, determining a sample expression score for the biomarker panel, comparing the sample expression score to the threshold expression score, wherein if the expression score is equal to or above the threshold expression score the clinical prognosis is a good prognosis. In certain example embodiments, a good prognosis indicates increased survival rates compared to a subject with an expression score below the threshold score. In certain example embodiments, the subject suffers from cancer. The cancer may include, but is not limited to, ovarian cancer, breast cancer, colon cancer, colorectal cancer, or glioblastoma. In certain example embodiments, the cancer is ovarian cancer. In certain other example embodiments, the ovarian cancer is high grade serous ovarian cancer. In certain example embodiments, the subject may receive, has received and/or will receive a chemotherapeutic treatment. The chemotherapeutic treatment may include administration of a platinum-based chemotherapeutic agent, an alkylating agent, an anti-metabolite, an anti-tumor antibiotic, a topoisomerase inhibitor, a mitotic inhibitor, or a combination thereof. In certain example embodiments, the chemotherapeutic treatment comprises administration of a platinum-based chemotherapeutic agent, a mitotic inhibitor, or a combination thereof. In certain other example embodiments, the chemotherapeutic treatment comprises administration of carboplatin and paclitaxel. In one example embodiment, the subject has high grade serous ovarian cancer and may receive, has received and/or will receive a platinum-based chemotherapeutic agent and a mitotic inhibitor, such as taxane. In another example embodiment, the subject has high grade serous ovarian cancer and is may receive, has received, and/or will receive carboplatin and paclitaxel.

[0024] In another aspect, the present invention relates to kits for conventional diagnostic uses listed above such as qPCR, NGS, microarray, and immunoassays such as immunohistochemistry, ELISA, Western blot and the like. Such kits include appropriate reagents and directions to assay the expression of the genes or gene products and quantify mRNA or protein expression.

[0025] Also disclosed are methods for identifying human tumors with or without the non-angiogenesis phenotype. In certain example embodiments, such methods may be used to identify patients that are sensitive to and respond to drugs that inhibit, either directly or indirectly, processes relating to angiogenesis. In certain other example embodiments, such methods may be used to identify patients that are resistant to or do not respond or will respond in adverse fashion to drugs that inhibit, either directly or indirectly, processes relating to angiogenesis.

[0026] This invention also relates to guiding effective treatment of patients. Further, methods relating to selection of patient treatment regimens and selecting patients for clinical trials of current, or developmental stage drugs that directly or indirectly affect angiogenesis are provided.

[0027] In addition, methods that accommodate the use of archived formalin fixed paraffin-embedded (FFPE) biopsy material, as well as fresh/frozen (FF) tissue, for assay of all transcripts, and are therefore compatible with the most widely available type of biopsy material, are described herein. A biomarker expression level may be determined using RNA obtained from FFPE tissue, fresh frozen tissue or fresh tissue that has been stored in solutions such as RNAlater®.

BRIEF DESCRIPTION OF DRAWINGS

[0028] FIG. 1 provides a heat map showing unsupervised hierarchical clustering of gene expression data in 265 high grade serous ovarian carcinomas. Each column represents the expression of these probe sets in one tumor. Probe set expression across all clusters is represented horizontally. The bar above the heat map is color-coded by cluster as described in the legend box. The second bar is color-coded for class label as described in the legend box. Functional processes corresponding to each probe set cluster are labeled to the right of the figure.

[0029] FIG. 2 provides Kaplan-Meier analysis of overall survival by cluster from unsupervised analysis of gene expression in 265 high grade serous ovarian carcinomas.

[0030] FIG. 3 provides Kaplan-Meier analysis of survival of the two classes defined by the 63-gene signature classifier in the Edinburgh (discovery) dataset. Proangiogenic group consists of Angio and Angioimmune subgroups. A. Progression-free survival. B. Overall survival.

[0031] FIG. 4 provides Kaplan-Meier analysis of survival of the two classes defined by the 63-gene signature classifier in the Tothill (validation) dataset. Proangiogenic group consists of Angio and Angioimmune subgroups. A. Progression-free survival. B. Overall survival.

[0032] FIG. 5 provides Kaplan Meier curves for progression free survival in Immune (FIG. 5A) and Proangiogenic (FIG. 5B) subgroups of the patients in the ICON7 trial cohort. Within each figure the survival differences are displayed across the 2 randomized treatment groups: 1) Carboplatin plus paclitaxel chemotherapy and 2) Carboplatin plus paclitaxel chemotherapy plus bevacizumab.

[0033] FIG. 6 provides Kaplan Meier curves for overall survival in Immune (FIG. 6A) and Proangiogenic (FIG. 6A) subgroups of patients in the ICON7 trial cohort. Within each figure the survival differences are displayed across the 2 randomized treatment groups: 1) Carboplatin plus paclitaxel chemotherapy and 2) Carboplatin plus paclitaxel chemotherapy plus bevacizumab.

[0034] FIG. 7 provides Kaplan Meier curves for progression free survival (A) and overall survival (B) for carboplatin and paclitaxel treated ICON7 trial patients defined by the 63 gene signature.

[0035] FIGS. 8A and 8B are graphs demonstrating certain classification performance benchmarks of an example non-angiogenesis signature as applied to colorectal cancer samples.

[0036] FIG. 9: Signature development: AUC of training set under CV.

[0037] FIG. 10: Signature development: C-Index of training set under CV.

[0038] FIG. 11: Signature development: HR of training set under CV.

[0039] FIG. 12: Signature development: HR of ICON7 SOC samples under CV.

[0040] FIG. 13: Signature development: C-Index of ICON7 SOC samples under CV.

[0041] FIG. 14: Signature development: HR of ICON7 Immune samples under CV.

[0042] FIG. 15: Signature development: HR of ICON7 ProAngio samples under CV.

[0043] FIG. 16: Core set analysis: Immune63GeneSig_CoreGenes_InternalVal.png.

[0044] FIG. 17: Core set analysis: Immune63GeneSig_CoreGenes_Tohtill.png.

[0045] FIG. 18: Core set analysis: Immune63GeneSig_CoreGenes_ICON7_SOC.png.

[0046] FIG. 19: Minimum gene set analysis: Immune63GeneSig_MinGenes_Tohtill.png

[0047] FIG. 20: ICON7 SOC: Minimum gene set analysis: Immune63GeneSig_MinGenes_ICON7_SOC.png.

[0048] FIG. 21: ICON7 Immune: Minimum gene set analysis: Immune63GeneSig_MinGenes_ICON7_Immune.png

[0049] FIG. 22: Kaplan Meier to show the differences in progression free survival probability between the samples predicted as Angio-Off (inactive) versus those that are predicted as Angio-On (active) by the 63 gene signature

[0050] FIG. 23: Semi-supervised hierarchical clustering of the 529 CRC samples published by Marrisa et al (2013) using the angiogenesis defining gene list.

[0051] FIG. 24: ROC Curve showing the discrimination in 63 gene signature scores between the angiogenesis active subtype and angiogenesis inactive subtype in the Marissa CRC data.

[0052] FIG. 25: Kaplan Meier Curve showing the survival differences between the angiogenesis active and angiogenesis inactive patients (treated only) as predicted by the 63 gene signature in the GSE14333 CRC data.

DETAILED DESCRIPTION OF THE INVENTION

[0053] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Definitions of common terms in molecu-

lar biology may be found in Benjamin Lewin, *Genes IX*, published by Jones and Bartlet, 2008 (ISBN 0763752223); Kendrew et al. (eds.), *The Encyclopedia of Molecular Biology*, published by Blackwell Science Ltd., 1994 (ISBN 0632021829); Robert A. Meyers (ed.), *Molecular Biology and Biotechnology: a Comprehensive Desk Reference*, published by VCH Publishers, Inc., 1995 (ISBN 9780471185710); Singleton et al., *Dictionary of Microbiology and Molecular Biology* 2nd ed., J. Wiley & Sons (New York, N.Y. 1994), and March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure* 4th ed., John Wiley & Sons (New York, N.Y. 1992).

[0054] The singular terms “a,” “an,” and “the” include plural referents unless context clearly indicates otherwise. Similarly, the word “or” is intended to include “and” unless the context clearly indicates otherwise. The term “comprises” means “includes.” In case of conflict, the present specification, including explanations of terms, will control.

[0055] As used herein terms “biomarker panel,” “expression classifier,” “classifier,” “expression signature,” or “signature” may be used interchangeably. The panel typically includes a plurality of biomarkers but may include only a single biomarker where that biomarker is useful individually in the methods of the invention.

[0056] All publications, published patent documents, and patent applications cited in this application are indicative of the level of skill in the art(s) to which the application pertains. All publications, published patent documents, and patent applications cited herein are hereby incorporated by reference to the same extent as though each individual publication, published patent document, or patent application was specifically and individually indicated as being incorporated by reference.

Overview

[0057] A major goal of current research efforts in cancer is to increase the efficacy of perioperative systemic therapy in patients by incorporating molecular parameters into clinical therapeutic decisions. Pharmacogenetics/genomics is the study of genetic/genomic factors involved in an individuals’ response to a foreign compound or drug. Agents or modulators which have a stimulatory or inhibitory effect on expression of a biomarker of the invention can be administered to individuals to treat (prophylactically or therapeutically) cancer in the patient. It is ideal to also consider the pharmacogenomics of the individual in conjunction with such treatment. Differences in metabolism of therapeutics may possibly lead to severe toxicity or therapeutic failure by altering the relationship between dose and blood concentration of the pharmacologically active drug. Thus, understanding the pharmacogenomics of an individual permits the selection of effective agents (e.g., drugs) for prophylactic or therapeutic treatments. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the level of expression of a biomarker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

[0058] The present invention relates to a molecular diagnostic tests useful for diagnosing cancers from different anatomical sites that includes the use of one or more common subtypes related to angiogenesis. The invention includes expression signatures that identify a subject as having a good or poor clinical prognosis, and expression

signatures that indicate whether to administer an anti-angiogenic therapeutic agent to a subject. The expression signature is derived by obtaining the expression profiles of samples from a sample set of known pathology and/or clinical outcome. The samples may originate from the same sample tissue type or different tissue types. As used herein an “expression profile” comprises a set of values representing the expression level for each biomarker analyzed from a given sample.

[0059] The expression profiles from the sample set are then analyzed using a mathematical model. Different mathematical models may be applied and include, but are not limited to, models from the fields of pattern recognition (Duda et al. *Pattern Classification*, 2nd ed., John Wiley, New York 2001), machine learning (Scholkopf et al. *Learning with Kernels*, MIT Press, Cambridge 2002, Bishop, *Neural Networks for Pattern Recognition*, Clarendon Press, Oxford 1995), statistics (Hastie et al. *The Elements of Statistical Learning*, Springer, New York 2001), bioinformatics (Dudoit et al., 2002, *J. Am. Statist. Assoc.* 97:77-87, Tibshirani et al., 2002, *Proc. Natl. Acad. Sci. USA* 99:6567-6572) or chemometrics (Vandeginste, et al., *Handbook of Chemometrics and Qualimetrics, Part B*, Elsevier, Amsterdam 1998). The mathematical model identifies one or more biomarkers expressed in the sample set that are most predictive of a given disease phenotype. These one or more biomarkers define an expression signature. Accordingly, an expression signature includes the biomarkers identified as most predictive of a given disease phenotype. In certain example embodiments, the mathematical model defines a variable, such as a weight, for each identified biomarker. In certain example embodiments, the mathematical model defines a decision function. The decision function may further define a threshold score which separates the sample set into two disease phenotypes such as, but not limited to, samples that have a good and poor clinical prognosis. In one example embodiment, the decision function and expression signature are defined using a linear classifier.

[0060] To classify new samples using a defined expression signature, the biomarkers defined by the expression signature, also referred to as a biomarker panel, are isolated and an expression profile of the biomarker panel determined. The new sample biomarker panel expression profile is analyzed with the same mathematical model used to define the expression signature. The biomarker panel may comprise one or more of the biomarkers defined by the expression signature. The biomarker panel may comprise one or more of the biomarkers defined by the expression signature. In certain example embodiments, the biomarker panel comprises one or more of the biomarkers listed in Table 2. In certain other example embodiments, the biomarker panel comprises all of the biomarkers listed in Table 2. In certain example embodiments, the biomarker panel comprises one or more of the biomarkers listed in Table 2. In certain other example embodiments, the biomarker panel comprises all of the biomarkers listed in Table 2. In certain example embodiments, the mathematical model defines an expression score for the new sample. The expression score may be determined by combining the expression values of the biomarkers with corresponding scalar weights using non-linear, algebraic, trigonometric or correlative means to derive a single scalar value. The expression score is compared to the threshold score and the sample classified based on whether the expression score is greater than, or equal to, or less than

the threshold score. In certain example embodiments, a sample expression score equal to or greater than the threshold score indicates a subject has a good clinical prognosis, and a sample expression score below the threshold score indicates a subject has a poor clinical prognosis. In certain example embodiments, a sample expression score equal to or greater than the threshold score indicates a subject has the signature. This may indicate a good clinical prognosis. A sample expression score below the threshold score indicates a subject does not have the signature. This may indicate a poor clinical prognosis.

[0061] One application of the expression signatures disclosed herein is the identification of patients with a good and poor clinical prognosis. The good or poor prognosis may be determined in the context of a certain treatment background (such as carboplatin/paclitaxel therapy as discussed herein). For example, the subject may be receiving or have received a standard chemotherapeutic treatment for the subject's cancer type. Given a treatment background, the expression signatures disclosed herein may also be used to determine whether an additional therapeutic agent, such as an anti-angiogenic therapeutic agent, should be administered to the patient. By examining the expression of at least one, optionally a collection of the identified biomarkers in a tumor, it is possible to determine the likely clinical outcomes of a patient. By examining the expression of at least one, optionally a collection of biomarkers, it is therefore possible to identify those patients in most need of more aggressive therapeutic regimens and likewise eliminate unnecessary therapeutic treatments or those unlikely to significantly improve or possibly harm a patient's clinical outcome. The present invention relates to prediction of clinical prognosis using at least progression free survival or overall survival rates. Accordingly, a "good prognosis" indicates a subject population with a cancer subtype that demonstrates an increased survival rate compared to other cancer subtypes, whereas a "poor prognosis" or "bad prognosis" indicates a subject population with a cancer subtype that demonstrates decreased survival rate compared to other cancer subtypes. Additional prognostic factors that may be considered are ethnicity and race, age, stage of disease, histology, tumor grade, tumor makers (for example, CA125), site-specific surgical treatment, size of residual disease, and tumor response. In certain example embodiments, a subject with an expression score equal to or above the threshold score is classified as having the non-angiogenesis subtype. In another example embodiment, a subject with a sample expression score above the threshold score is classified as having a good clinical prognosis. In yet another example embodiment, a subject with a sample expression score above or equal to the threshold score indicates the subject will likely experience a detrimental effect, or have a poorer clinical prognosis, if administered an anti-angiogenic therapeutic agent.

[0062] In certain example embodiments, the determination of a subject's clinical prognosis or selection of an additional therapeutic agent may be made in the context of past, current, or planned chemotherapeutic treatment. For example, the subject may set to start, be currently receiving, or have just completed, a standard of care chemotherapeutic treatment for the cancer type of the subject. In certain example embodiments, the chemotherapeutic treatment may include administration of an alkylating agent, an anti-metabolite, a platinum-based drug, an anti-tumor antibiotic, a

topoisomerase inhibitor, a mitotic inhibitor, a corticosteroid, a hormone based therapeutic, or a combination thereof. Example alkylating agents include nitrogen mustards, nitrosoureas, alkyl sulfonates, triazines, and ethylenimines. Example platinum drugs include cisplatin, carboplatin, and oxaloplatin. Example anti-metabolites include 5-fluorouracil, 6-mercaptopurine, capecitabine, cladribine, clofarabine, cytarabine, floxuridine, fludarabine, gemcitabine, hydroxyurea, methotrexate, pemetrexed, pentostatin, and thioguanine. Example anti-tumor antibiotics include daunorubicin, doxorubicin, epirubicin, idarubicin, actinomycin-D, bleomycin, mitomycin-C, and mitoxantrone. Example topoisomerase inhibitors include topotecan, irinotecan, etoposide, and teniposide. Example mitotic inhibitors include taxanes, epothilones, vinca alkaloids, and estramustine. Example corticosteroids include prednisone, methylprednisolone, and dexamethasone. In certain example embodiments the chemotherapy may include treatment with L-asparaginase, imatinib, gefitinib, sunitinib, bortezomib, retinoids, tretinoin, bexaroten, arsenic trioxide, flukestrant, tamoxifen, toremifene, anastrozole, exemestane, letrozole, progestins, estrogens, bicalutamide, flutamide, nilutamide, gonadotropin-releasing hormone agonists or analogs, rituximab, alemtuzumab, BCG, interleukin-2, interferon-alfa, thalidomide, and lenalidomide.

[0063] In certain example embodiments the chemotherapeutic treatment may comprise a cyclophosphamide, methotrexate, and fluorouracil (CMF) treatment regimen, a cyclophosphamide, doxorubicin, and fluorouracil (CAF) treatment regimen, an epirubicin and cyclophosphamide (EC) treatment regimen, a fluorouracil, epirubicin, and cyclophosphamide (FEC) treatment regimen, a paclitaxel and cyclophosphamide treatment regimen, a paclitaxel and carboplatin treatment regimen, a doxorubicin and cyclophosphamide treatment regimen, or a doxorubicin and paclitaxel treatment regimen. In one example embodiment, the neoadjuvant cancer therapy comprises a platinum based chemotherapy treatment regimen. In one example embodiment, the platinum-based chemotherapy treatment regimen comprises paclitaxel and carboplatin.

[0064] Another application of the expression signatures disclosed herein is the stratification of response to, and selection of patients for therapeutic drug classes that encompass anti-angiogenic therapies. By examining the expression of a collection of the identified biomarkers in a tumor, it is possible to determine which therapeutic agent or combination of agents will be most likely to reduce the growth rate of a cancer. It is also possible to determine which therapeutic agent or combination of agents will be the least likely to reduce the growth rate of a cancer and/or which may cause adverse affects and thus be contra-indicated. By examining the expression of a collection of biomarkers, it is therefore possible to eliminate ineffective or inappropriate therapeutic agents. Importantly, in certain embodiments, these determinations can be made on a patient-by-patient basis or on an agent-by-agent basis. Thus, one can determine whether or not a particular therapeutic regimen is likely to benefit a particular patient or type of patient, and/or whether a particular regimen should be continued. The present invention provides a test that can guide therapy selection as well as selecting patient groups for enrichment strategies during clinical trial evaluation of novel therapeutics. For example, when evaluating a putative anti-angiogenic agent or treatment regime, the expression signatures and methods dis-

closed herein may be used to select individuals for clinical trials that have cancer subtypes that are responsive to anti-angiogenic agents.

[0065] A cancer is “responsive” to a therapeutic agent if its rate of growth is inhibited as a result of contact with the therapeutic agent, compared to its growth in the absence of contact with the therapeutic agent. Growth of a cancer can be measured in a variety of ways. For instance, the size of a tumor or measuring the expression of tumor markers appropriate for that tumor type. In one example embodiment, the expression signature disclosed herein may determine a patient’s clinical prognosis upon administration of an anti-angiogenic agent following standard of care chemotherapeutic therapy for the cancer type of the patient.

[0066] A cancer is “non-responsive” to a therapeutic agent if its rate of growth is not inhibited, or inhibited to a very low degree, as a result of contact with the therapeutic agent when compared to its growth in the absence of contact with the therapeutic agent. As stated above, growth of a cancer can be measured in a variety of ways, for instance, the size of a tumor or measuring the expression of tumor markers appropriate for that tumor type. The quality of being non-responsive to a therapeutic agent is a highly variable one, with different cancers exhibiting different levels of “non-responsiveness” to a given therapeutic agent, under different conditions. Still further, measures of non-responsiveness can be assessed using additional criteria beyond growth size of a tumor such as, but not limited to, patient quality of life, and degree of metastases.

[0067] The angiogenesis subtype can be identified from a fresh/frozen (FF) or formalin fixed paraffin embedded (FFPE) patient sample. In one example embodiment, the cancer type is ovarian cancer, breast cancer, colon cancer, colorectal cancer, lung cancer, prostate cancer, or glioblastoma. In another example embodiment, the cancer type is an ovarian cancer. In a further example embodiment, the cancer type is breast cancer. In another example embodiment, the cancer type is lung cancer. In another example embodiment, the cancer type is colon cancer. In another example embodiment, the cancer type is prostate cancer. In another example embodiment, the cancer type is glioblastoma.

Identifying Expression Signatures

[0068] The expression signatures of the present invention are identified by analyzing the expression profiles of certain biomarkers in a patient sample set. Biomarkers suitable for use in the present invention include DNA, RNA, and proteins. In one example embodiment, biomarkers suitable for use in the present invention include RNA and cDNA. The biomarkers are isolated from a patient sample and their expression levels determined to derive a set of expression profiles for each sample analyzed in the patient sample set. In certain example embodiments the expression signature identifies a non-angiogenesis phenotype observed in cancer tissues, identified as a signature score for a combination of biomarkers above or equal to a threshold, the phenotype characterized by an up-regulation of immune response related genes and a down-regulation of genes associated with angiogenesis or vasculature development related processes.

[0069] a. Expression Profiles

[0070] In certain embodiments, the expression profile obtained is a genomic or nucleic acid expression profile, where the amount or level of one or more nucleic acids in the

sample is determined. In these embodiments, the sample that is assayed to generate the expression profile employed in the diagnostic or prognostic methods is a nucleic acid sample. The nucleic acid sample includes a population of nucleic acids that includes the expression information of the phenotype determinative biomarkers of the cell or tissue being analyzed. In some embodiments, the nucleic acid may include RNA or DNA nucleic acids, e.g., mRNA, cRNA, cDNA etc., so long as the sample retains the expression information of the host cell or tissue from which it is obtained. The sample may be prepared in a number of different ways, as is known in the art, e.g., by mRNA isolation from a cell, where the isolated mRNA is used as isolated, amplified, or employed to prepare cDNA, cRNA, etc., as is known in the field of differential gene expression. Accordingly, determining the level of mRNA in a sample includes preparing cDNA or cRNA from the mRNA and subsequently measuring the cDNA or cRNA. The sample is typically prepared from a cell or tissue harvested from a subject in need of treatment, e.g., via biopsy of tissue, using standard protocols, where cell types or tissues from which such nucleic acids may be generated include any tissue in which the expression pattern of the to be determined phenotype exists, including, but not limited to, disease cells or tissue, body fluids, etc.

[0071] The expression profile may be generated from the initial nucleic acid sample using any convenient protocol. While a variety of different manners of generating expression profiles are known, such as those employed in the field of differential gene expression/biomarker analysis, one representative and convenient type of protocol for generating expression profiles is array-based gene expression profile generation protocols. Such applications are hybridization assays in which a nucleic acid that displays “probe” nucleic acids for each of the genes to be assayed/profiled in the profile to be generated is employed. In these assays, a sample of target nucleic acids is first prepared from the initial nucleic acid sample being assayed, where preparation may include labeling of the target nucleic acids with a label, e.g., a member of a signal producing system. Following target nucleic acid sample preparation, the sample is contacted with the array under hybridization conditions, whereby complexes are formed between target nucleic acids that are complementary to probe sequences attached to the array surface. The presence of hybridized complexes is then detected, either qualitatively or quantitatively. Specific hybridization technology which may be practiced to generate the expression profiles employed in the subject methods includes the technology described in U.S. Pat. Nos. 5,143, 854; 5,288,644; 5,324,633; 5,432,049; 5,470,710; 5,492, 806; 5,503,980; 5,510,270; 5,525,464; 5,547,839; 5,580, 732; 5,661,028; 5,800,992; the disclosures of which are herein incorporated by reference; as well as WO 95/21265; WO 96/31622; WO 97/10365; WO 97/27317; EP 373 203; and EP 785 280. In these methods, an array of “probe” nucleic acids that includes a probe for each of the biomarkers whose expression is being assayed is contacted with target nucleic acids as described above. Contact is carried out under hybridization conditions, e.g., stringent hybridization conditions as described above, and unbound nucleic acid is then removed. The resultant pattern of hybridized nucleic acids provides information regarding expression for each of the biomarkers that have been probed, where the expression information is in terms of whether or not the gene

is expressed and, typically, at what level, where the expression data, i.e., expression profile, may be both qualitative and quantitative.

[0072] b. Diseases and Sample Tissue Sources

[0073] In certain example embodiments, the patient sample comprises a cancer tissue samples, such as an archived sample. The patient sample is preferably derived from cancer tissue and may be from a sample having been characterized by prognosis, likelihood of recurrence, long term survival, clinical outcome, treatment response, diagnosis, cancer classification, or personalized genomics profile. As used herein cancer includes, but is not limited to, leukemia, brain cancer, prostate cancer, liver cancer, ovarian cancer, stomach cancer, colorectal cancer, throat cancer, breast cancer, skin cancer, melanoma, lung cancer, sarcoma, cervical cancer, testicular cancer, bladder cancer, endocrine cancer, endometrial cancer, esophageal cancer, glioma, lymphoma, neuroblastoma, osteosarcoma, pancreatic cancer, pituitary cancer, renal cancer, and the like. As used herein, colorectal cancer encompasses cancers that may involve cancer in tissues of both the rectum and other portions of the colon as well as cancers that may be individually classified as either colon cancer or rectal cancer. In one embodiment, the methods described herein refer to cancers that are treated with anti-angiogenic agents, anti-angiogenic targeted therapies, inhibitors of angiogenesis signaling, but not limited to these classes. These cancers also include subclasses and subtypes of these cancers at various stages of pathogenesis. In certain example embodiments, the patient sample comprises an ovarian cancer sample. In certain example embodiments, the ovarian cancer sample is a serous ovarian cancer sample such as a high grade serous ovarian cancer sample. In another example embodiment, the patient sample comprises a breast cancer sample. In yet another example embodiment, the patient sample comprises a glioblastoma sample.

[0074] “Biological sample”, “sample”, and “test sample” are used interchangeably herein to refer to any material, biological fluid, tissue, or cell obtained or otherwise derived from an individual. This includes blood (including whole blood, leukocytes, peripheral blood mononuclear cells, buffy coat, plasma, and serum), sputum, tears, mucus, nasal washes, nasal aspirate, breath, urine, semen, saliva, meningeal fluid, amniotic fluid, glandular fluid, lymph fluid, nipple aspirate, bronchial aspirate, synovial fluid, joint aspirate, ascites, cells, a cellular extract, and cerebrospinal fluid. This also includes experimentally separated fractions of all of the preceding. For example, a blood sample can be fractionated into serum or into fractions containing particular types of blood cells, such as red blood cells or white blood cells (leukocytes). If desired, a sample can be a combination of samples from an individual, such as a combination of a tissue and fluid sample. The term “biological sample” also includes materials containing homogenized solid material, such as from a stool sample, a tissue sample, or a tissue biopsy, for example. The term “biological sample” also includes materials derived from a tissue culture or a cell culture, including tissue resection and biopsy samples. Any suitable methods for obtaining a biological sample can be employed; example methods include, e.g., phlebotomy, swab (e.g., buccal swab), and a fine needle aspirate biopsy procedure. Samples can also be collected, e.g., by micro dissection (e.g., laser capture micro dissection (LCM) or laser micro dissection (LMD)), bladder wash, smear (e.g., a

PAP smear), or ductal lavage. A “biological sample” obtained or derived from an individual includes any such sample that has been processed in any suitable manner after being obtained from the individual, for example, fresh frozen or formalin fixed and/or paraffin embedded. The methods of the invention as defined herein may begin with an obtained sample and thus do not necessarily incorporate the step of obtaining the sample from the patient. The methods may be in vitro methods performed on an isolated sample.

[0075] As used herein, the term “patient” includes human and non-human animals. The preferred patient for treatment is a human. “Patient,” “individual” and “subject” are used interchangeably herein.

[0076] c. Biomarkers

[0077] As used herein, the term “biomarker” can refer to a gene, an mRNA, cDNA, an antisense transcript, a miRNA, a polypeptide, a protein, a protein fragment, or any other nucleic acid sequence or polypeptide sequence that indicates either gene expression levels or protein production levels. When a biomarker indicates or is a sign of an abnormal process, disease or other condition in an individual, that biomarker is generally described as being either over-expressed or under-expressed as compared to an expression level or value of the biomarker that indicates or is a sign of a normal process, an absence of a disease or other condition in an individual. “Up-regulation”, “up-regulated”, “over-expression”, “over-expressed”, and any variations thereof are used interchangeably to refer to a value or level of a biomarker in a biological sample that is greater than a value or level (or range of values or levels) of the biomarker that is typically detected in similar biological samples from healthy or normal individuals. The terms may also refer to a value or level of a biomarker in a biological sample that is greater than a value or level (or range of values or levels) of the biomarker that may be detected at a different stage of a particular disease.

[0078] “Down-regulation”, “down-regulated”, “under-expression”, “under-expressed”, and any variations thereof are used interchangeably to refer to a value or level of a biomarker in a biological sample that is less than a value or level (or range of values or levels) of the biomarker that is typically detected in similar biological samples from healthy or normal individuals. The terms may also refer to a value or level of a biomarker in a biological sample that is less than a value or level (or range of values or levels) of the biomarker that may be detected at a different stage of a particular disease.

[0079] Further, a biomarker that is either over-expressed or under-expressed can also be referred to as being “differentially expressed” or as having a “differential level” or “differential value” as compared to a “normal” expression level or value of the biomarker that indicates or is a sign of a normal process or an absence of a disease, disease subtype, or other condition in an individual. Thus, “differential expression” of a biomarker can also be referred to as a variation from a “normal” expression level of the biomarker.

[0080] The terms “differential biomarker expression” and “differential expression” are used interchangeably to refer to a biomarker whose expression is activated to a higher or lower level in a subject suffering from a specific disease, relative to its expression in a normal subject, or relative to its expression in a patient that responds differently to a particular therapy or has a different prognosis. The terms

also include biomarkers whose expression is activated to a higher or lower level at different stages of the same disease. It is also understood that a differentially expressed biomarker may be either activated or inhibited at the nucleic acid level or protein level, or may be subject to alternative splicing to result in a different polypeptide product. Such differences may be evidenced by a variety of changes including mRNA levels, miRNA levels, antisense transcript levels, or protein surface expression, secretion or other partitioning of a polypeptide. Differential biomarker expression may include a comparison of expression between two or more genes or their gene products; or a comparison of the ratios of the expression between two or more genes or their gene products; or even a comparison of two differently processed products of the same gene, which differ between normal subjects and subjects suffering from a disease; or between various stages of the same disease. Differential expression includes both quantitative, as well as qualitative, differences in the temporal or cellular expression pattern in a biomarker among, for example, normal and diseased cells, or among cells which have undergone different disease events or disease stages.

[0081] In certain example embodiments, the biomarker is an RNA transcript. As used herein “RNA transcript” refers to both coding and non-coding RNA, including messenger RNAs (mRNA), alternatively spliced mRNAs, ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNAs (snRNA), and antisense RNA. Measuring mRNA in a biological sample may be used as a surrogate for detection of the level of the corresponding protein and gene in the biological sample. Thus, any of the biomarkers or biomarker panels described herein can also be detected by detecting the appropriate RNA. Methods of biomarker expression profiling include, but are not limited to quantitative PCR, NGS, northern blots, southern blots, microarrays, SAGE, immunoassays (ELISA, EIA, agglutination, nephelometry, turbidimetry, Western blot, immunoprecipitation, immunocytochemistry, flow cytometry, Luminex assay), and mass spectrometry. The overall expression data for a given sample may be normalized using methods known to those skilled in the art in order to correct for differing amounts of starting material, varying efficiencies of the extraction and amplification reactions.

[0082] In certain example embodiments, biomarkers useful for distinguishing between cancer subtypes that demonstrate a good clinical prognosis and a poor clinical prognosis and can be determined by identifying biomarkers exhibiting the highest degree of variability between samples in the patient data set as determined using the expression detection methods and patient sample sets discussed above. Standard statistical methods known in the art for identifying highly variable data points in expression data may be used to identify the highly variable biomarkers. For example, a combined background and variance filter to the patient data set. The background filter is based on the selection of probe sets with expression E and expression variance var_E above the thresholds defined by background standard deviation σ_{Bg} (from the Expression Console software) and quantile of the standard normal distribution z_α at a specified significance a probe sets were kept if:

$$E > \log_2(z_\alpha \sigma_{Bg}); \log_2(\text{var}_E) > 2[\log_2(\sigma_{Bg}) - E - \log_2(\log(2))]$$

[0083] where α defines a significance threshold. In certain example embodiment, the significance threshold is $6.3 \cdot 10^{-5}$.

In another example embodiment, the significance threshold may be between $1.0 \cdot 10^{-7}$ to $1.0 \cdot 10^{-3}$.

[0084] In certain example embodiments, the highly variable biomarkers may be further analyzed to group samples in the patient data set into subtypes or clusters based on similar gene expression profiles. For examples, biomarkers may be clustered based on how highly correlated the up-regulation or down-regulation of their expression is to one another. Various clustering analysis techniques known in the art may be used. In one example embodiment, hierarchical agglomerative clustering is used to identify the cancer subtypes. To determine the biological relevance of each subtype, the biomarkers within each cluster may be further mapped to their corresponding genes and annotated by cross-reference to one or more gene ontology databases containing information on biological activity and biological pathways associated with the gene. In another example embodiment, biomarkers in clusters that are up regulated and enriched for immune response general functional terms are grouped into a putative non-angiogenesis sample group and used for expression signature generation. In another example embodiment, biomarkers in clusters that are down regulated and enriched for angiogenesis and vasculature development and are up regulated and enriched for immune response general functional terms are grouped into a putative non-angiogenesis sample group and used for expression signature generation. Further details for conducting functional analysis of biomarker clusters is provided in the Examples section below.

[0085] In one example embodiment, the biomarkers useful in deriving an expression signature for use in the present invention are those biomarkers listed in Table 1. These biomarkers are identified as having predictive value to determine a patient response to a therapeutic agent and/or a prognostic value in identifying individuals with a good or poor clinical prognosis.

[0086] In certain example embodiments, the expression of the biomarkers disclosed herein correlates with whether a patient will experience a detrimental or beneficial effect from administration of an anti-angiogenic therapeutic agent. By examining the expression of a collection of biomarkers, it is therefore possible to eliminate ineffective or inappropriate therapeutic agents. Importantly, in certain embodiments, these determinations can be made on a patient-by-patient basis or on an agent-by-agent basis. Thus, one can determine whether or not a particular therapeutic regimen is likely to benefit a particular patient or type of patient, and/or whether a particular regimen should be continued.

[0087] In certain other example embodiments, the expression of the biomarkers disclosed herein correlate with a patient's overall clinical prognosis. By examining the expression of a collection of biomarkers identified in a tumor, it is possible to determine whether the individual has a cancer subtype associated with good clinical prognosis or poor clinical prognosis. Importantly, in certain embodiments, these determinations can be made on a patient-by-patient basis. Thus, one of ordinary skill in the art can use predicted prognosis to help select appropriate treatment regimens to treat the underlying disease while eliminating those treatment regimens most likely to produce undesired or medically unwarranted adverse side effects.

[0088] The SEQ ID NOs listed in Table 1 refer to probe set identifiers used to measure the expression levels of the genes on an example transcriptome array. Expression signatures of

the present invention have been cross-validated using expression data from different arrays with different probe sets as detailed further in the Examples section below. Accordingly, the expression signatures and methods disclosed herein are not limited to expression values measured using the probe sets disclosed herein.

TABLE 1

Genes in Clusters of FIG. 1		
SEQ NO:	Orientation	Gene Symbol
1	Sense (Fully Exonic)	PDGFC
2	Sense (Fully Exonic)	TGFB3
3	Sense (Fully Exonic)	RAC2
4	Sense (Fully Exonic)	MARCKS
5	Sense (Fully Exonic)	ALOX5
6	Sense (Fully Exonic)	COL8A1
7	Sense (Fully Exonic)	KCNAB2
8	Sense (Fully Exonic)	THBS1
9	Sense (Fully Exonic)	CTGF
10	Sense (Fully Exonic)	CTGF
11	Sense (Fully Exonic)	VCAN
12	Sense (Fully Exonic)	IGKC
13	Sense (Fully Exonic)	IGKC
14	Sense (includes Intronic)	NFATC1
15	Sense (Fully Exonic)	HMHA1
16	Sense (Fully Exonic)	FCGR1B
17	Sense (Fully Exonic)	EDA2R
18	Sense (Fully Exonic)	COL8A1
19	Sense (Fully Exonic)	COL12A1
20	Sense (Fully Exonic)	HLA-B
21	Sense	HLA-F
22	Sense (Fully Exonic)	EGR1
23	Sense (Fully Exonic)	SULF2
24	Sense (Fully Exonic)	CERCAM
25	Sense (Fully Exonic)	ATF3
26	Sense (Fully Exonic)	MIR21
27	Sense (Fully Exonic)	IFTT2
28	Sense (Fully Exonic)	IGLC3
29	Sense (Fully Exonic)	IGLC3
30	Sense (Fully Exonic)	IGLC3
31	Sense (Fully Exonic)	IGLC3
32	Sense (Fully Exonic)	IGLC3
33	Sense (Fully Exonic)	IGLC3
34	Sense (Fully Exonic)	ANGPTL2
35	Sense (Fully Exonic)	COL5A2
36	Sense (Fully Exonic)	THY1
37	Sense (Fully Exonic)	NDN
38	Sense (Fully Exonic)	RGS2
39	Sense (Fully Exonic)	MEIS3P2
40	Sense (Fully Exonic)	GBP2
41	Sense (Fully Exonic)	FAT1
42	Sense (Fully Exonic)	COL1A1
43	Sense (Fully Exonic)	MMP11
44	Sense (Fully Exonic)	GADD45B
45	Sense (Fully Exonic)	MMP14
46	Sense (Fully Exonic)	IGHG4
47	Sense (Fully Exonic)	HCLS1
48	No Transcript match	
49	Sense (Fully Exonic)	JAM3
50	Sense (Fully Exonic)	TMEM49
51	Sense (Fully Exonic)	LTBP2
52	Sense (Fully Exonic)	IRS1
53	Sense (Fully Exonic)	C17orf91
54	Sense (Fully Exonic)	GPNMB
55	Sense (Fully Exonic)	FAM198B
56	Sense (Fully Exonic)	CHST15
57	Sense (Fully Exonic)	DCN
58	Sense (Fully Exonic)	VCAM1
59	Sense (Fully Exonic)	CIITA
60	Sense (Fully Exonic)	GAS7
61	Sense (Fully Exonic)	COL3A1
62	Sense (Fully Exonic)	ITGB2
63	Sense (Fully Exonic)	ELN
64	Sense (Fully Exonic)	CMTM3

TABLE 1-continued

Genes in Clusters of FIG. 1		
SEQ NO:	Orientation	Gene Symbol
65	Sense (Fully Exonic)	ANTXR1
66	Sense (Fully Exonic)	IL4I1
67	Sense (Fully Exonic)	ANTXR2
68	Sense (Fully Exonic)	IGLC2 /// IGLC3
69	Sense (Fully Exonic)	IGLC3
70	Sense (Fully Exonic)	BST2
71	Sense (Fully Exonic)	COL10A1
72	Sense (Fully Exonic)	IGLC3
73	Sense (Fully Exonic)	FBP1
74	Sense (Fully Exonic)	RHOBTB3
75	Sense (Fully Exonic)	CD74
76	Sense (Fully Exonic)	ISM1
77	Sense (Fully Exonic)	CSRNP1
78	Sense (Fully Exonic)	DCN
79	Sense (Fully Exonic)	IGFBP4
80	Sense (Fully Exonic)	CCDC80
81	Sense (Fully Exonic)	COL3A1
82	Sense (Fully Exonic)	ZFP36
83	Sense (Fully Exonic)	MMP11
84	Sense (Fully Exonic)	COL1A2
85	Sense (Fully Exonic)	HLA-DPA1
86	Sense (Fully Exonic)	TWIST1
87	Sense (Fully Exonic)	ZNF154
88	Sense (Fully Exonic)	IGLC3
89	Sense (Fully Exonic)	IGKC
90	Sense (Fully Exonic)	IGHG1
91	Sense (Fully Exonic)	COL1A2
92	Sense (Fully Exonic)	APOC1
93	AntiSense	EGR1
94	Sense (Fully Exonic)	KIAA0146
95	Sense (Fully Exonic)	TPM1
96	Sense (includes Intronic)	DMD
97	No Transcript match	
98	Sense (Fully Exonic)	DUSP1
99	Sense (Fully Exonic)	GBP1
100	Sense (includes Intronic)	PDGFC
101	Sense (includes Intronic)	MSN
102	Sense (includes Intronic)	TPM1
103	Sense (Fully Exonic)	EMB
104	Sense (Fully Exonic)	FOS
105	Sense (includes Intronic)	DPYSL3
106	AntiSense	EGR1
107	AntiSense	NRP2
108	Sense (Fully Exonic)	MMP2
109	Sense (Fully Exonic)	CTGF
110	Sense (Fully Exonic)	ACTA2
111	Sense (Fully Exonic)	LOXL1
112	Sense (Fully Exonic)	CDH11
113	Sense (Fully Exonic)	LUM
114	Sense (Fully Exonic)	NNMT
115	Sense (Fully Exonic)	GJA1
116	AntiSense	CTHRC1
117	Sense (Fully Exonic)	CTSB
118	Sense (Fully Exonic)	PLAU
119	Sense (Fully Exonic)	PDGFRA
120	Sense (Fully Exonic)	VCAN
121	AntiSense	—
122	Sense (Fully Exonic)	IGHG4 /// IGHG2 /// IGHG1 ///I GHGP
123	Sense (Fully Exonic)	IGHG2
124	Sense (includes Intronic)	C3orf26
125	AntiSense	ATF3
126	AntiSense	ATF3
127	Sense (Fully Exonic)	FN1
128	AntiSense	CALD1
129	AntiSense	CALD1
130	AntiSense	EGR1
131	AntiSense	TWIST1
132	AntiSense	TWIST1
133	AntiSense	BATF2
134	AntiSense	NFKBIZ
135	Sense (includes Intronic)	C3orf26
136	AntiSense	LOXL1

TABLE 1-continued

Genes in Clusters of FIG. 1		
SEQ NO:	Orientation	Gene Symbol
137	Sense (includes Intronic)	—
138	AntiSense	FN1
139	AntiSense	COL1A1
140	Sense (Fully Exonic)	TREH
141	AntiSense	APOL1
142	Sense (Fully Exonic)	COL10A1
143	Sense (Fully Exonic)	GAL3ST4
144	Sense (Fully Exonic)	TAGLN
145	Sense (Fully Exonic)	TWIST1
146	Sense (Fully Exonic)	HCLS1
147	Sense (Fully Exonic)	ITGB2
148	Sense (Fully Exonic)	HLA-B
149	Sense (Fully Exonic)	C17orf91
150	Sense (Fully Exonic)	FBLIM1
151	Sense (Fully Exonic)	COL15A1
152	Sense (Fully Exonic)	AQP7P3
153	AntiSense	IGFBP5
154	Sense (Fully Exonic)	FANK1
155	AntiSense	INS
156	Sense (Fully Exonic)	COL27A1
157	Sense (Fully Exonic)	COL5A1
158	Sense (Fully Exonic)	PRICKLE2
159	Sense (Fully Exonic)	N/A
160	Sense (Fully Exonic)	GXYLT2
161	Sense (includes Intronic)	KLF12
162	No Transcript match	
163	Sense (Fully Exonic)	FBXO32
164	No Transcript match	
165	Sense (Fully Exonic)	ASAH2B
166	AntiSense	PPFIBP1
167	AntiSense	XIST
168	Sense (Fully Exonic)	IGFBP6
169	Sense (Fully Exonic)	ROBO1
170	Sense (Fully Exonic)	TPM1
171	AntiSense	N/A
172	AntiSense	PLEKHG1
173	Sense (Fully Exonic)	NR2F1
174	Sense (Fully Exonic)	NPDC1
175	AntiSense	INS
176	Sense (Fully Exonic)	TRAF5
177	Sense (Fully Exonic)	CALD1
178	Sense (includes Intronic)	CHRM3
179	Sense (Fully Exonic)	AMOTL1
180	Sense (includes Intronic)	COL12A1
181	Sense (Fully Exonic)	PLXNA4
182	Sense (includes Intronic)	TMEM43
183	Sense (includes Intronic)	RORA
184	AntiSense	INS
185	Sense (Fully Exonic)	TSPAN18
186	No Transcript match	
187	Sense (Fully Exonic)	TNC
188	Sense (Fully Exonic)	TYRO3
189	AntiSense	EFNA5
190	Sense (Fully Exonic)	MYL9
191	Sense (Fully Exonic)	MIR198
192	Sense (includes Intronic)	N/A
193	Sense (includes Intronic)	PLA2R1
194	Sense (Fully Exonic)	COL14A1
195	Sense (Fully Exonic)	NRP1
196	Sense (Fully Exonic)	FSCN1
197	Sense (includes Intronic)	PDGFD
198	No Transcript match	
199	Sense (includes Intronic)	DOCK4
200	Sense (Fully Exonic)	TRIM13
201	Sense (Fully Exonic)	IGFBP5
202	Sense (Fully Exonic)	C19orf63
203	AntiSense	KLF6
204	AntiSense	TRIO
205	Sense (Fully Exonic)	COL4A1
206	Sense (Fully Exonic)	EPDR1
207	Sense (Fully Exonic)	FNDC1
208	Sense (Fully Exonic)	IL1R1
209	Sense (Fully Exonic)	CES4

TABLE 1-continued

Genes in Clusters of FIG. 1		
SEQ NO:	Orientation	Gene Symbol
210	Sense (Fully Exonic)	GPR176
211	Sense (includes Intronic)	GXYLT2
212	AntiSense	WHSC1L1
213	Sense (Fully Exonic)	N/A
214	Sense (Fully Exonic)	RGN
215	Sense (includes Intronic)	CA3
216	Sense (Fully Exonic)	TIMP3
217	Sense (Fully Exonic)	EFNA5
218	Sense (Fully Exonic)	RASGRF2
219	Sense (includes Intronic)	RELL1
220	AntiSense	ACSS3
221	Sense (Fully Exonic)	STMN3
222	Sense (Fully Exonic)	N/A
223	AntiSense	C7orf29
224	Sense (Fully Exonic)	HOXC6
225	Sense (Fully Exonic)	KLF8
226	Sense (includes Intronic)	SERINC5
227	Sense (Fully Exonic)	AKT3
228	Sense (Fully Exonic)	TGFB2
229	AntiSense	WNT5A
230	No Transcript match	
231	No Transcript match	
232	AntiSense	IGFBP7
233	No Transcript match	
234	Sense (includes Intronic)	SULT1C4
235	Sense (Fully Exonic)	AASS
236	Sense (Fully Exonic)	HEPH
237	Sense (Fully Exonic)	ADH5
238	Sense (Fully Exonic)	TIMP2
239	Sense (Fully Exonic)	EMP1
240	Sense (Fully Exonic)	CXCL14
241	Sense (Fully Exonic)	ZNF548
242	Sense (Fully Exonic)	SGCB
243	Sense (includes Intronic)	ASH2L
244	Sense (includes Intronic)	SERINC5
245	No Genome match	
246	Sense (Fully Exonic)	TMEM159
247	Sense (includes Intronic)	RBMS3
248	Sense (Fully Exonic)	TMEM49
249	Sense (includes Intronic)	RORA
250	No Transcript match	
251	AntiSense	ZNF608
252	No Genome match	
253	Sense (Fully Exonic)	ADAMTS2
254	Sense (Fully Exonic)	APCDD1
255	AntiSense	GXYLT2
256	Sense (Fully Exonic)	XIST
257	Sense (Fully Exonic)	MBNL2
258	Sense (Fully Exonic)	SHF
259	Sense (includes Intronic)	APBB2
260	No Transcript match	
261	Sense (Fully Exonic)	COL14A1
262	Sense (Fully Exonic)	IGFBP5
263	Sense (Fully Exonic)	CREB5
264	AntiSense	INS
265	Sense (Fully Exonic)	BAHCC1
266	Sense (Fully Exonic)	RFXAP
267	Sense (Fully Exonic)	INS
268	Sense (Fully Exonic)	DDR2
269	Sense (Fully Exonic)	CA12
270	Sense (Fully Exonic)	RHOB
271	Sense (Fully Exonic)	N/A
272	Sense (Fully Exonic)	SNORD116-4
273	Sense (Fully Exonic)	MEG3
274	Sense (Fully Exonic)	WNT4
275	Sense (Fully Exonic)	FBLN2
276	AntiSense	DAAM1
277	No Transcript match	
278	Sense (Fully Exonic)	CHN1
279	Sense (includes Intronic)	APBB2
280	Sense (Fully Exonic)	PTRF
281	AntiSense	IGF1
282	Sense (Fully Exonic)	UST

TABLE 1-continued

Genes in Clusters of FIG. 1		
SEQ NO:	Orientation	Gene Symbol
283	Sense (Fully Exonic)	SMARCA1
284	Sense (includes Intronic)	N/A
285	Sense (Fully Exonic)	IGLC3
286	AntiSense	INS
287	Sense (Fully Exonic)	KANK4
288	AntiSense	IGF1
289	Sense (Fully Exonic)	CYP27A1
290	AntiSense	EIF2B5
291	No Transcript match	
292	Sense (Fully Exonic)	SNRNP25
293	Sense (Fully Exonic)	SETD7
294	Sense (Fully Exonic)	MSX1
295	Sense (Fully Exonic)	HOPX
296	Sense (Fully Exonic)	NID2
297	Sense (Fully Exonic)	IGF1
298	Sense (Fully Exonic)	PSD3
299	Sense (Fully Exonic)	FGFR1
300	Sense (Fully Exonic)	ETV1
301	Sense (Fully Exonic)	ZNF655
302	No Genome match	
303	AntiSense	INS
304	Sense (Fully Exonic)	SFRP2
305	Sense (Fully Exonic)	SPAG16
306	AntiSense	NR2F2
307	Sense (includes Intronic)	SYNPO2
308	Sense (Fully Exonic)	FAM101B
309	AntiSense	IGF2
310	Sense (Fully Exonic)	CA3
311	Sense (Fully Exonic)	XIST
312	No Transcript match	
313	Sense (Fully Exonic)	WNT7A
314	Sense (includes Intronic)	N/A
315	Sense (Fully Exonic)	FGFR1
316	AntiSense	FXVD6
317	Sense (Fully Exonic)	FGFR1
318	Sense (includes Intronic)	IGFBP7
319	Sense (Fully Exonic)	TIMP2
320	Sense (Fully Exonic)	DUSP1
321	Sense (includes Intronic)	SERINC5
322	No Transcript match	
323	Sense (Fully Exonic)	ABLIM1
324	Sense (Fully Exonic)	ARL4A
325	AntiSense	SH3TC2
326	AntiSense	NR2F2
327	Sense (Fully Exonic)	ENG
328	Sense (Fully Exonic)	MGP
329	Sense (Fully Exonic)	MEG3
330	AntiSense	FAM115A
331	Sense (Fully Exonic)	EGR1
332	Sense (Fully Exonic)	SNORD116-3
333	Sense (Fully Exonic)	AEBP1
334	Sense (includes Intronic)	SDK1
335	Sense (Fully Exonic)	ENC1
336	Sense (Fully Exonic)	SNORD116-7
337	Sense (Fully Exonic)	N/A
338	Sense (Fully Exonic)	APOD
339	AntiSense	N/A
340	AntiSense	GAS1
341	Sense (Fully Exonic)	VPS36
342	No Transcript match	
343	Sense (Fully Exonic)	SPHK2
344	Sense (Fully Exonic)	SNORD116-8
345	Sense (Fully Exonic)	MYO10
346	Sense (Fully Exonic)	HOXC6
347	Sense (Fully Exonic)	RNF149
348	Sense (Fully Exonic)	BTG2
349	Sense (includes Intronic)	MAP3K1
350	Sense (Fully Exonic)	SNORD116-23
351	Sense (includes Intronic)	ACSL4
352	Sense (Fully Exonic)	CYP27C1
353	Sense (includes Intronic)	COL12A1
354	Sense (Fully Exonic)	IGFBP5
355	Sense (Fully Exonic)	DUSP4

TABLE 1-continued

Genes in Clusters of FIG. 1		
SEQ NO:	Orientation	Gene Symbol
356	Sense (Fully Exonic)	PFKFB3
357	Sense (Fully Exonic)	SDC2
358	AntiSense	FXVD6
359	Sense (Fully Exonic)	COL5A1
360	Sense (Fully Exonic)	MARCKS
361	Sense (Fully Exonic)	IRS2
362	Sense (Fully Exonic)	N/A
363	AntiSense	FSCN1
364	Sense (Fully Exonic)	FYN
365	Sense (Fully Exonic)	IGFBP5
366	Sense (Fully Exonic)	NUDT4P1
367	Sense (Fully Exonic)	NFKBIZ
368	Sense (Fully Exonic)	N/A
369	Sense (Fully Exonic)	C7orf41
370	Sense (Fully Exonic)	MEG3
371	Sense (Fully Exonic)	N/A
372	Sense (Fully Exonic)	PLEKHG1
373	Sense (Fully Exonic)	ZNF827
374	Sense (Fully Exonic)	ZNF175
375	Sense (Fully Exonic)	XIST
376	Sense (includes Intronic)	GSN
377	Sense (includes Intronic)	RORA
378	Sense (Fully Exonic)	CA13
379	AntiSense	TMX4
380	Sense (Fully Exonic)	KIT
381	Sense (includes Intronic)	WDR78
382	Sense (Fully Exonic)	ECEL1
383	Sense (Fully Exonic)	XIST
384	Sense (Fully Exonic)	PROCR
385	Sense (Fully Exonic)	C9orf167
386	Sense (Fully Exonic)	MUC6
387	Sense (includes Intronic)	P4HA2
388	Sense (Fully Exonic)	FAM69C
389	Sense (Fully Exonic)	NOX4
390	Sense (includes Intronic)	N/A
391	No Transcript match	
392	Sense (Fully Exonic)	SMOX
393	Sense (Fully Exonic)	KIAA0922
394	No Transcript match	
395	Sense (Fully Exonic)	XIST
396	Sense (Fully Exonic)	NPAS2
397	Sense (Fully Exonic)	NAV1
398	Sense (includes Intronic)	N/A
399	Sense (Fully Exonic)	HLA-A
400	Sense (Fully Exonic)	FAM46C
401	Sense (Fully Exonic)	N/A
402	Sense (Fully Exonic)	SLAMF7
403	Sense (Fully Exonic)	FCER1G
404	Sense (Fully Exonic)	C1S
405	Sense (Fully Exonic)	NUPR1
406	AntiSense	C1QC
407	AntiSense	SAT1
408	Sense (Fully Exonic)	SOD2
409	Sense (Fully Exonic)	IRF1
410	Sense (Fully Exonic)	SFN
411	AntiSense	LTB
412	Sense (Fully Exonic)	ARID5A
413	Sense (Fully Exonic)	BST2
414	Sense (Fully Exonic)	HLA-F
415	Sense (Fully Exonic)	XAF1
416	Sense (Fully Exonic)	TCOF1
417	Sense (Fully Exonic)	RPL23AP1
418	Sense (Fully Exonic)	IL1RN
419	Sense (Fully Exonic)	IFIT5
420	Sense (Fully Exonic)	B2M
421	AntiSense	GBP1
422	Sense (Fully Exonic)	HLA-F
423	Sense (Fully Exonic)	DGKA
424	Sense (Fully Exonic)	XBP1
425	Sense (Fully Exonic)	PLCG2
426	Sense (Fully Exonic)	FAM46C
427	No Genome match	
428	Sense (Fully Exonic)	TREM2

TABLE 1-continued

Genes in Clusters of FIG. 1		
SEQ NO:	Orientation	Gene Symbol
429	Sense (Fully Exonic)	LGALS9
430	Sense (Fully Exonic)	HLA-DPB1
431	AntiSense	ODF3B
432	Sense (Fully Exonic)	MX1
433	Sense (Fully Exonic)	STAT1
434	Sense (Fully Exonic)	CTSB
435	Sense (Fully Exonic)	FAM26F
436	Sense (includes Intronic)	PARP14
437	AntiSense	SAT1
438	Sense (Fully Exonic)	CTSS
439	No Transcript match	
440	Sense (Fully Exonic)	CTSB
441	Sense (Fully Exonic)	ADAM8
442	Sense (includes Intronic)	B2M
443	Sense (Fully Exonic)	FLVCR2
444	Sense (Fully Exonic)	TYROBP
445	AntiSense	SAMD9L
446	Sense (Fully Exonic)	SAMD9L
447	Sense (Fully Exonic)	SIGLEC1
448	Sense (Fully Exonic)	MMP7
449	Sense (Fully Exonic)	APOL1
450	Sense (Fully Exonic)	CYLD
451	Sense (Fully Exonic)	HLA-B
452	Sense (Fully Exonic)	SAT1
453	Sense (Fully Exonic)	C1QB
454	Sense (Fully Exonic)	HLA-DMB
455	Sense (Fully Exonic)	NLRCS
456	Sense (Fully Exonic)	FAM20A
457	AntiSense	N/A
458	Sense (Fully Exonic)	STAT1
459	Sense (includes Intronic)	STAT1
460	Sense (Fully Exonic)	STAT1
461	AntiSense	N/A
462	Sense (Fully Exonic)	DERL3
463	Sense (Fully Exonic)	HLA-F
464	Sense (Fully Exonic)	MAFB
465	Sense (Fully Exonic)	CD4
466	Sense (Fully Exonic)	HLA-A
467	Sense (Fully Exonic)	UBE2L6
468	Sense (Fully Exonic)	C1QC
469	Sense (Fully Exonic)	CD163
470	Sense (Fully Exonic)	LRMP
471	Sense (Fully Exonic)	C11orf17
472	Sense (Fully Exonic)	XAF1
473	Sense (Fully Exonic)	GLRX
474	Sense (Fully Exonic)	IFIH1
475	Sense (Fully Exonic)	CD44
476	Sense (Fully Exonic)	LITAF
477	Sense (Fully Exonic)	CCDC69
478	Sense (Fully Exonic)	GBP5
479	Sense (Fully Exonic)	PML
480	Sense (Fully Exonic)	SAMD9
481	Sense (Fully Exonic)	CBR3
482	Sense (Fully Exonic)	RASGRP2
483	Sense (Fully Exonic)	FCGR2A
484	Sense (Fully Exonic)	BST2
485	Sense (Fully Exonic)	HLA-A
486	Antisense	COL1A1
487	No Genome Match	
488	No Genome Match	

[0089] In certain example embodiments, all or a portion of the biomarkers recited in Table 1 may be used in an expression signature. For example, expression signatures comprising the biomarkers in Table 1 can be generated using the methods provided herein and can comprise between one, and all of the markers set forth in Tables 1 and each and every combination in between (e.g., four selected markers, 16 selected markers, 74 selected markers, etc.). In some embodiments, the expression signature comprises at least 5, 10, 20, 40, 60, 100, 150, 200, or 300 or more markers. In

other embodiments, the predictive biomarker panel comprises no more than 5, 10, 20, 40, 60, 100, 150, 200, 300, 400, 500, 600 or 700 markers. In one example embodiment, the expression signature includes a plurality of markers listed in Table 1. In some embodiments the expression signature includes at least about 1%, about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, or about 99% of the markers listed in Table 1. Selected expression signatures can be assembled from the biomarkers provided using methods described herein and analogous methods known in the art. In one embodiment, the expression signature contains all genes or gene products in Table 1.

[0090] 4. Mathematical Models

[0091] The following methods may be used to derive expression signatures for distinguishing between subjects that are responsive or non-responsive to anti-angiogenic therapeutics, or as prognostic indicators of certain cancer types, including expression signatures derived from the biomarkers disclosed above. In certain other example embodiments, the expression signature is derived using a decision tree (Hastie et al. The Elements of Statistical Learning, Springer, New York 2001), a random forest (Breiman, 2001 Random Forests, Machine Learning 45:5), a neural network (Bishop, Neural Networks for Pattern Recognition, Clarendon Press, Oxford 1995), discriminant analysis (Duda et al. Pattern Classification, 2nd ed., John Wiley, New York 2001), including, but not limited to linear, diagonal linear, quadratic and logistic discriminant analysis, a Prediction Analysis for Microarrays (PAM, (Tibshirani et al., 2002, Proc. Natl. Acad. Sci. USA 99:6567-6572)) or a Soft Independent Modeling of Class Analogy analysis. (SIMCA, (Wold, 1976, Pattern Recogn. 8:127-139)).

[0092] Biomarker expression values may be defined in combination with corresponding scalar weights on the real scale with varying magnitude, which are further combined through linear or non-linear, algebraic, trigonometric or correlative means into a single scalar value via an algebraic, statistical learning, Bayesian, regression, or similar algorithms which together with a mathematically derived decision function on the scalar value provide a predictive model by which expression profiles from samples may be resolved into discrete classes of responder or non-responder, resistant or non-resistant, to a specified drug, drug class, molecular subtype, or treatment regimen. Such predictive models, including biomarker membership, are developed by learning weights and the decision threshold, optimized for sensitivity, specificity, negative and positive predictive values, hazard ratio or any combination thereof, under cross-validation, bootstrapping or similar sampling techniques, from a set of representative expression profiles from historical patient samples with known drug response and/or resistance.

[0093] In one embodiment, the biomarkers are used to form a weighted sum of their signals, where individual weights can be positive or negative. The resulting sum ("expression score") is compared with a pre-determined reference point or value. The comparison with the reference point or value may be used to diagnose, or predict a clinical condition or outcome.

[0094] As described above, one of ordinary skill in the art will appreciate that the biomarkers included in the classifier provided in Tables 1 will carry unequal weights in a classifier for determining clinical prognosis. Therefore, while as

few as one biomarker may be used to diagnose or predict an clinical prognosis or response to a therapeutic agent, the specificity and sensitivity or diagnosis or prediction accuracy may increase using more biomarkers.

[0095] As used herein, the term “weight” refers to the absolute magnitude of an item in a statistical calculation. The weight of each biomarker in a gene expression classifier may be determined on a data set of patient samples using learning methods known in the art. As used herein the term “bias” or “offset” refers to a constant term derived using the mean expression of the signatures genes in a training set and is used to mean-center the each gene analyzed in the test dataset.

[0096] In certain example embodiments, the expression signature is defined by a decision function. A decision function is a set of weighted expression values derived using a linear classifier. All linear classifiers define the decision function using the following equation:

$$f(x)=w'x \quad b=\sum w_i x_i + b \quad (1)$$

[0097] All measurement values, such as the microarray gene expression intensities x_i , for a certain sample are collected in a vector x . Each intensity is then multiplied with a corresponding weight w_i to obtain the value of the decision function $f(x)$ after adding an offset term b . In deriving the decision function, the linear classifier will further define a threshold value that splits the gene expression data space into two disjoint sections. Example linear classifiers include but are not limited to partial least squares (PLS), (Nguyen et al., *Bioinformatics* 18 (2002) 39-50), support vector machines (SVM) (Schölkopf et al., *Learning with Kernels*, MIT Press, Cambridge 2002), and shrinkage discriminant analysis (SDA) (Ahdesmäki et al., *Annals of applied statistics* 4, 503-519 (2010)). In one example embodiment, the linear classifier is a PLS linear classifier.

[0098] The decision function is empirically derived on a large set of training samples, for example from patients showing a good or poor clinical prognosis. The threshold separates a patient group based on different characteristics such as, but not limited to, clinical prognosis before or after a given therapeutic treatment. The interpretation of this quantity, i.e. the cut-off threshold, is derived in the development phase (“training”) from a set of patients with known outcome. The corresponding weights and the responsiveness/resistance cut-off threshold for the decision score are fixed a priori from training data by methods known to those skilled in the art. In one example embodiment, Partial Least Squares Discriminant Analysis (PLS-DA) is used for determining the weights. (L. Stähle, S. Wold, *J. Chemom.* 1 (1987) 185-196; D. V. Nguyen, D. M. Rocke, *Bioinformatics* 18 (2002) 39-50).

[0099] Effectively, this means that the data space, i.e. the set of all possible combinations of biomarker expression values, is split into two mutually exclusive groups corresponding to different clinical classifications or predictions, for example, one corresponding to good clinical prognosis and poor clinical prognosis. In the context of the overall classifier, relative over-expression of a certain biomarker can either increase the decision score (positive weight) or reduce it (negative weight) and thus contribute to an overall decision of, for example, a good clinical prognosis.

[0100] In certain example embodiments of the invention, the data is transformed non-linearly before applying a weighted sum as described above. This non-linear transfor-

mation might include increasing the dimensionality of the data. The non-linear transformation and weighted summation might also be performed implicitly, for example, through the use of a kernel function. (Schölkopf et al. *Learning with Kernels*, MIT Press, Cambridge 2002).

[0101] In certain example embodiments, the patient training set data is derived by isolated RNA from a corresponding cancer tissue sample set and determining expression values by hybridizing the isolated RNA to a microarray. In certain example embodiments, the microarray used in deriving the expression signature is a transcriptome array. As used herein a “transcriptome array” refers to a microarray containing probe sets that are designed to hybridize to sequences that have been verified as expressed in the diseased tissue of interest. Given alternative splicing and variable poly-A tail processing between tissues and biological contexts, it is possible that probes designed against the same gene sequence derived from another tissue source or biological context will not effectively bind to transcripts expressed in the diseased tissue of interest, leading to a loss of potentially relevant biological information. Accordingly, it is beneficial to verify what sequences are expressed in the disease tissue of interest before deriving a microarray probe set. Verification of expressed sequences in a particular disease context may be done, for example, by isolating and sequencing total RNA from a diseased tissue sample set and cross-referencing the isolated sequences with known nucleic acid sequence databases to verify that the probe set on the transcriptome array is designed against the sequences actually expressed in the diseased tissue of interest. Methods for making transcriptome arrays are described in United States Patent Application Publication No. 2006/0134663, which is incorporated herein by reference. In certain example embodiments, the probe set of the transcriptome array is designed to bind within 300 nucleotides of the 3' end of a transcript. Methods for designing transcriptome arrays with probe sets that bind within 300 nucleotides of the 3' end of target transcripts are disclosed in United States Patent Application Publication No. 2009/0082218, which is incorporated by reference herein. In certain example embodiments, the microarray used in deriving the gene expression profiles of the present invention is the Almac Ovarian Cancer DSA™ microarray (Almac Group, Craigavon, United Kingdom).

[0102] An optimal linear classifier can be selected by evaluating a linear classifier's performance using such diagnostics as “area under the curve” (AUC). AUC refers to the area under the curve of a receiver operating characteristic (ROC) curve, both of which are well known in the art. AUC measures are useful for comparing the accuracy of a classifier across the complete data range. Linear classifiers with a higher AUC have a greater capacity to classify unknowns correctly between two groups of interest (e.g., ovarian cancer samples and normal or control samples). ROC curves are useful for plotting the performance of a particular feature (e.g., any of the biomarkers described herein and/or any item of additional biomedical information) in distinguishing between two populations (e.g., individuals responding and not responding to a therapeutic agent). Typically, the feature data across the entire population (e.g., the cases and controls) are sorted in ascending order based on the value of a single feature. Then, for each value for that feature, the true positive and false positive rates for the data are calculated. The true positive rate is determined by counting the number of cases above the value for that feature and then dividing by

the total number of positive cases. The false positive rate is determined by counting the number of controls above the value for that feature and then dividing by the total number of controls. Although this definition refers to scenarios in which a feature is elevated in cases compared to controls, this definition also applies to scenarios in which a feature is lower in cases compared to the controls (in such a scenario, samples below the value for that feature would be counted). ROC curves can be generated for a single feature as well as for other single outputs, for example, a combination of two or more features can be mathematically combined (e.g., added, subtracted, multiplied, etc.) to provide a single sum value, and this single sum value can be plotted in a ROC curve. Additionally, any combination of multiple features, in which the combination derives a single output value, can be plotted in a ROC curve. These combinations of features may comprise a test. The ROC curve is the plot of the true positive rate (sensitivity) of a test against the false positive rate (1-specificity) of the test.

[0103] In one example embodiment an angiogenesis expression signature is directed to the 63 biomarkers detailed in Table 2 with corresponding ranks, and weights and associated bias detailed in the table or alternative rankings, and weightings and bias, depending, for example, on the disease setting. Table 2 ranks the biomarkers in order of absolute decreasing weight, in an example classifier, in the compound decision score function. The methods of the invention may rely upon measuring one or more, up to all, of the biomarkers listed in table 2. The methods of the invention may comprise measuring the expression levels of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 40, 50, 60 or each of the biomarkers from Table 2. In certain embodiments the method may comprise measuring the expression levels of 2 to 5 of the biomarkers from Table 2.

TABLE 2

63 Biomarker Signature			
Rank	Gene Symbol	Weight	Bias
1	IGF2	-0.01737	9.8884
2	SOX11	-0.01457	4.5276
3	INS	-0.01409	7.0637
4	CXCL17	0.012568	4.8478
5	SLC5A1	0.012426	4.8920
6	TMEM45A	-0.0124	6.1307
7	CXCR2P1	0.011427	3.1478
8	MFAP2	-0.01039	9.0516
9	MATN3	-0.01028	3.7313
10	RTP4	0.010052	4.9852
11	COL3A1	-0.01002	8.4130
12	CDR1	-0.00916	8.1778
13	RARRES3	0.009056	6.8964
14	TNFSF10	0.008876	6.2325
15	NUAK1	-0.0087	6.6771
16	SNORD114-14	-0.00864	5.6385
17	SRPX	-0.00862	5.0850
18	SPARC	-0.00848	6.0135
19	GBJ1	0.008445	5.8142
20	TIMP3	-0.00823	6.5937
21	ISLR	-0.0079	8.9876
22	TUBA1A	-0.00754	9.6540
23	DEXI	0.007271	5.5913
24	BASP1	-0.00724	8.4396
25	PXDN	-0.00724	7.7570
26	GBP4	0.007226	3.1119
27	SLC28A3	0.007201	4.2125
28	HLA-DRA	0.007197	8.3089

TABLE 2-continued

63 Biomarker Signature			
Rank	Gene Symbol	Weight	Bias
29	TAP2	0.007189	4.8464
30	ACSL5	0.007155	6.8703
31	CDH11	-0.00708	4.9925
32	PSMB9	0.006962	4.1122
33	MMP14	-0.00683	10.1689
34	CD74	0.006825	9.2707
35	LOXL1	-0.00676	9.6429
36	CHTA	0.006623	5.5396
37	ZNF697	-0.00658	7.0319
38	SH3RF2	0.006549	5.0029
39	MIR198	-0.00654	5.1935
40	COL1A2	-0.00645	6.0427
41	TNFRSF14	0.006421	9.0366
42	COL8A1	-0.00642	6.4565
43	C21orf63	0.006261	5.9811
44	TAP1	0.006215	8.6458
45	PDPN	-0.00612	5.3198
46	RHOBTB3	-0.00597	3.5609
47	BCL11A	0.005943	4.3818
48	HLA-DOB	0.005851	4.6075
49	XAF1	0.005742	7.9229
50	ARHGAP26	0.005632	4.3991
51	POLD2	-0.00558	9.4183
52	DPYSL2	-0.00533	8.3469
53	COL4A1	-0.0052	7.0317
54	ID3	-0.00516	7.5673
55	CFB	0.005077	5.7951
56	NID1	-0.00494	4.7186
57	FKBP7	-0.00489	2.9437
58	TIMP2	-0.00468	7.5253
59	RCBTB1	-0.00458	7.4491
60	ANGPTL2	-0.00448	5.6807
61	ENTPD7	-0.00442	7.3772
62	SHISA4	-0.00403	6.0601
63	HINT1	0.003651	6.0724

[0104] In another example embodiment an angiogenesis expression signature is directed to the 63 biomarkers detailed in Table 3 with corresponding ranks detailed in the table or alternative rankings depending, for example, on the disease setting. Table 3 ranks the biomarkers in order of absolute decreasing weight, in an example classifier, in the compound decision score function. The methods of the invention may rely upon measuring one or more, up to all, of the biomarkers listed in table 3. The methods of the invention may comprise measuring the expression levels of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 40, 50, 60 or each of the biomarkers from Table 3. In certain embodiments the methods may comprise measuring the expression levels of 2 to 5 of the biomarkers from Table 3.

TABLE 3

Gene	Total Delta HR	Rank
IGF2	0.048910407	1
CDR1	0.045335288	2
COL3A1	0.044869217	3
SPARC	0.043434096	4
TIMP3	0.042053053	5
INS	0.04013658	6
COL8A1	0.026780907	7
NUAK1	0.026752491	8
MATN3	0.02402318	9
TMEM45A	0.016999761	10
SRPX	0.016372168	11
CDH11	0.015604812	12

TABLE 3-continued

Gene	Total Delta HR	Rank
MMP14	0.014583388	13
LOXL1	0.010315358	14
PXDN	0.009728534	15
COL1A2	0.009267887	16
ANGPTL2	0.006071504	17
POLD2	0.004297935	18
NID1	0.00408724	19
ISLR	0.003014488	20
SNORD114-14	0.002992636	21
CXCR2P1	0.002804432	22
MIR198	0.002173041	23
BCL11A	0.001258286	24
PDPN	0.000989109	25
TNFRSF14	0.000132838	26
ENTPD7	6.25143E-05	27
HINT1	-0.000113156	28
TAP1	-0.000379242	29
ID3	-0.000452476	30
RCBTB1	-0.000695459	31
SOX11	-0.001068812	32
SHISA4	-0.001470801	33
COL4A1	-0.001714442	34
TUBA1A	-0.001817696	35
TIMP2	-0.004079263	36
FKBP7	-0.004575097	37
TAP2	-0.004597761	38
TNFSF10	-0.005307314	39
ZNF697	-0.007733496	40
CIITA	-0.008785689	41
BASP1	-0.009340492	42
XAF1	-0.009760794	43
DEXI	-0.009798099	44
SH3RF2	-0.009856754	45
HLA-DOB	-0.009987248	46
RHOBTB3	-0.010264542	47
GBP4	-0.010747831	48
DPYSL2	-0.012042179	49
ARHGAP26	-0.012380203	50
MFAP2	-0.013981916	51
CD74	-0.016415304	52
ACSL5	-0.016912224	53
SLC28A3	-0.016996213	54
GJB1	-0.018395345	55
C21orf63	-0.019853038	56
PSMB9	-0.020314379	57
HLA-DRA	-0.020436677	58
CFB	-0.022202886	59
RARRES3	-0.034723666	60
CXCL17	-0.038523986	61
SLC5A1	-0.042034346	62
RTP4	-0.045259104	63

[0105] Probesets that can be used to measure the expression of the biomarkers are shown in Table 4.

TABLE 4

Probeset	Gene	SEQ ID No.
OC3P.6916.C1_s_at	ACSL5	489
OC3P.5381.C1_s_at	ACSL5	490
OC3P.2679.C1_s_at	ANGPTL2	491
ADXStrongB12_at	ANGPTL2	N/A
OC3P.9834.C1_s_at	ANGPTL2	492
OCMX.9546.C1_x_at	ANGPTL2	493
OCADA.8226_s_at	ANGPTL2	494
OCADNP.8811_s_at	ANGPTL2	495
OCADA.3065_s_at	ARHGAP26	496
OCADA.1272_s_at	ARHGAP26	497
OC3SNGnh.16379_x_at	ARHGAP26	498
OCMX.11710.C1_at	ARHGAP26	499
OCADA.4396_s_at	ARHGAP26	500
OC3P.15451.C1_at	ARHGAP26	501

TABLE 4-continued

Probeset	Gene	SEQ ID No.
OC3SNGnh.16379_at	ARHGAP26	502
OC3SNGnh.17316_s_at	ARHGAP26	503
OCADA.964_s_at	ARHGAP26	504
OC3SNGnh.6403_s_at	ARHGAP26	505
OC3P.3912.C1_s_at	ARHGAP26	506
OC3P.2419.C1_s_at	BASP1	507
OCRS2.9952_s_at	BASP1	508
OCRS2.9952_x_at	BASP1	509
OCRS.854_s_at	BCL11A	510
OC3P.14938.C1_s_at	BCL11A	511
OCMX.12290.C1_at	BCL11A	512
OCADA.10230_s_at	BCL11A	513
OC3SNGnh.4343_at	BCL11A	514
OC3SNGnh.16766_x_at	BCL11A	515
OCMX.1680.C1_s_at	BCL11A	516
OC3P.14938.C1-334a_s_at	BCL11A	517
OCMX.12290.C1_x_at	BCL11A	518
OCADA.2850_s_at	BCL11A	519
OCADA.1135_s_at	C21orf63	520
OCMX.14248.C1_s_at	C21orf63	521
OC3P.14091.C1_s_at	C21orf63	522
OC3P.14431.C1_s_at	C21orf63	523
OCADA.8368_x_at	CD74	524
OC3SNGnh.19144_s_at	CD74	525
OC3P.104.CB1_x_at	CD74	526
OCADNP.1805_s_at	CD74	527
OC3SNG.3064-21a_x_at	CD74	528
OC3P.14147.C1_s_at	CDH11	529
OCADNP.10024_s_at	CDH11	530
OCHP.148_s_at	CDH11	531
OCADA.6210_s_at	CDH11	532
OC3SNGnh.5056_x_at	CDH11	533
OC3SNGnh.4032_s_at	CDH11	534
OCHPRC.58_s_at	CDH11	535
OCMX.1718.C1_s_at	CDH11	536
OCADA.8067_x_at	CDH11	537
OCADNP.8007_s_at	CDR1	538
OC3P.295.C1_s_at	CFB	539
ADXStrongB56_at	CFB	N/A
OC3P.295.C2_x_at	CFB	540
OC3SNGnh.14167_at	CFB	541
OC3SNGn.5914-165a_s_at	CFB	542
OC3SNGn.970-10a_s_at	CFB	543
OCADNP.9683_s_at	CFB	544
OC3P.295.C2_at	CFB	545
OC3SNGnh.14167_s_at	CFB	546
OCADNP.17538_s_at	CIITA	547
OC3P.805.C1_s_at	CIITA	548
OCEM.1780_s_at	CIITA	549
OC3SNGnh.16892_s_at	CIITA	550
OCADA.6540_s_at	CIITA	551
OCHP.1927_s_at	CIITA	552
OC3SNGn.354-123a_s_at	CIITA	553
OC3SNGnh.4794_at	CIITA	554
OC3SNGn.8474-50a_x_at	COL1A2	555
OCMX.184.C11_s_at	COL1A2	556
OC3SNG.115-2502a_at	COL1A2	557
OC3SNG.116-9169a_s_at	COL1A2	558
OC3P.60.CB2_x_at	COL1A2	559
OC3P.6454.C1_s_at	COL1A2	560
OC3SNG.115-2502a_x_at	COL1A2	561
OCMX.184.C16_x_at	COL1A2	562
OCHP.173_x_at	COL1A2	563
OC3P.60.CB1_x_at	COL1A2	564
OC3SNGn.2538-539a_x_at	COL1A2	565
OCMX.184.C16_s_at	COL1A2	566
OCADNP.4048_s_at	COL3A1	567
OC3P.81.CB2_s_at	COL3A1	568
OC3SNGnh.19127_s_at	COL3A1	569
OC3SNGn.1211-6a_s_at	COL3A1	570
OCADNP.11975_s_at	COL4A1	571
OC3P.850.C1-1145a_s_at	COL4A1	572
OCHPRC.29_s_at	COL4A1	573
OC3SNGnh.276_x_at	COL4A1	574
OC3SNGnh.18844_at	COL8A1	575

TABLE 4-continued

Probeset	Gene	SEQ ID No.
OC3P.1087.C1_s_at	COL8A1	576
OC3P.13652.C1_s_at	COL8A1	577
OCADNP.14932_s_at	COL8A1	578
OC3P.10562.C1_s_at	COL8A1	579
OCHPRC.94_s_at	CXCL17	580
OC3SNG.3604-23a_at	CXCR2P1	581
OC3SNG.3604-23a_x_at	CXCR2P1	582
OC3SNGnh.13095_s_at	DEXI	583
OC3P.7366.C1_s_at	DEXI	584
OCADA.2531_s_at	DEXI	585
OC3SNGnh.3527_s_at	DEXI	586
OC3P.10489.C1_s_at	DEXI	587
OCADNP.10600_s_at	DEXI	588
OCADA.1911_s_at	DPYSL2	589
OC3P.7322.C1_s_at	DPYSL2	590
OC3SNG.366-35a_s_at	ENTPD7	591
OC3SNGnh.5644_s_at	FKBP7	592
OC3SNGnh.17831_at	FKBP7	593
OCADNP.7326_s_at	FKBP7	594
OC3P.12003.C1_x_at	FKBP7	595
OC3P.4378.C1_s_at	GBP4	596
OC3SNGnh.5459_s_at	GBP4	597
OCADNP.3694_s_at	GBP4	598
OC3SNG.3671-13a_s_at	GJB1	599
2874688_at	HINT1	N/A
2874689_at	HINT1	N/A
Adx-200093_s_at	HINT1	600
OC3SNGnh.5235_x_at	HINT1	601
2874702_at	HINT1	N/A
2874727_at	HINT1	N/A
200093_s_at	HINT1	602
2874697_at	HINT1	N/A
2874725_at	HINT1	N/A
2874696_at	HINT1	N/A
2874737_at	HINT1	N/A
2874735_at	HINT1	N/A
Adx-200093-up_s_at	HINT1	603
OC3P.14829.C1_s_at	HLA-DOB	604
ADXBAD55_at	HLA-DOB	N/A
OC3P.674.C1_s_at	HLA-DRA	605
OCADNP.8307_s_at	HLA-DRA	606
OC3P.2407.C1_s_at	ID3	607
ADXGood100_at	IGF2	N/A
OC3SNG.899-20a_s_at	IGF2	608
OC3SNGn.5728-103a_x_at	IGF2	610
OC3P.4645.C1_s_at	IGF2	613
OC3SNGnh.19773_s_at	IGF2	614
OCADNP.10122_s_at	IGF2	615
OCADNP.7400_s_at	IGF2	616
ADXGood100_at	INS	N/A
OCADNP.17017_s_at	INS	609
OC3SNGn.5728-103a_x_at	INS	610
OCEM.2174_s_at	INS	611
OCEM.2035_x_at	INS	612
OC3P.4645.C1_s_at	INS	613
OC3SNGnh.19773_s_at	INS	614
OCADNP.10122_s_at	INS	615
OCADNP.7400_s_at	INS	616
OCEM.2035_at	INS	617
OC3P.9976.C1_x_at	ISLR	618
OCHP.1306_s_at	LOXL1	619
OCADA.10621_s_at	MA1N3	620
OC3P.2576.C1_x_at	MFAP2	621
OCHP.1079_s_at	MFAP2	622
OC3P.11139.C1_s_at	MIR198	623
OC3P.2111.C1_x_at	MIR198	624
ADXBAD7_at	MIR198	N/A
OCHP.462_s_at	MIR198	625
OC3SNGn.8954-766a_s_at	MIR198	626
OCADNP.4997_s_at	MIR198	627
OCHP.228_s_at	MMP14	628
OC3P.4123.C1_x_at	MMP14	629
OC3P.4123.C1_s_at	MMP14	630
OCADA.1433_x_at	NID1	631
OCADNP.7347_s_at	NID1	632

TABLE 4-continued

Probeset	Gene	SEQ ID No.
OC3P.3404.C1_s_at	NID1	633
OC3SNGn.3328-664a_s_at	NID1	634
OCADNP.9225_s_at	NUAK1	635
ADXStrongB87_at	NUAK1	N/A
OC3SNGn.2676-391a_s_at	NUAK1	636
OCHPRC.111_s_at	PDPN	637
OCADNP.10047_s_at	PDPN	638
OCHPRC.96_s_at	PDPN	639
OC3P.13523.C1_s_at	PDPN	640
OC3SNG.4571-22a_x_at	POLD2	641
OCEM.1126_s_at	POLD2	642
ADXGood4_at	POLD2	N/A
OC3SNGn.890-5a_s_at	POLD2	643
OC3P.14770.C1_s_at	PSMB9	644
OCSR.920_s_at	PSMB9	645
OC3P.4627.C1_s_at	PSMB9	646
OC3SNGnh.8187_at	PSMB9	647
OCMX.15283.C1_x_at	PSMB9	648
OCADNP.804_s_at	PSMB9	649
OC3SNGnh.8187_x_at	PSMB9	650
OCMX.14440.C1_x_at	PSMB9	651
OC3P.1307.C1_s_at	PXDN	652
OC3P.8838.C1_s_at	PXDN	653
OCHP.1891_s_at	RARRES3	654
OC3P.8963.C1_s_at	RCBTB1	655
OC3SNGnh.6721_x_at	RHOBTB3	656
OC3SNGnh.6912_x_at	RHOBTB3	657
OC3SNGnh.957_s_at	RHOBTB3	658
OC3SNG.2402-2883a_s_at	RHOBTB3	659
OCHPRC.1436_at	RHOBTB3	660
OC3SNGn.5382-76a_s_at	RHOBTB3	661
OC3SNGnh.957_x_at	RHOBTB3	662
OC3SNGnh.957_at	RHOBTB3	663
OC3P.12862.C1_s_at	RHOBTB3	664
OC3SNG.2401-1265a_x_at	RHOBTB3	665
OC3P.5737.C1_s_at	RHOBTB3	666
OCHP.1722_s_at	RTP4	667
OC3P.9552.C1-496a_s_at	RTP4	668
OC3P.9552.C1_x_at	RTP4	669
OC3P.9552.C1_at	RTP4	670
OC3SNGnh.865_s_at	SH3RF2	671
OC3SNGnh.16695_s_at	SH3RF2	672
OCADNP.12161_s_at	SH3RF2	673
OC3SNGn.439-184a_s_at	SH3RF2	674
OCHPRC.86_s_at	SH3RF2	675
OCADNP.2340_s_at	SHISA4	676
OC3SNG.6118-43a_s_at	SHISA4	677
OCADNP.8940_s_at	SLC28A3	678
OC3SNGnh.971_s_at	SLC28A3	679
OCADA.4025_s_at	SLC28A3	680
OC3P.9666.C1_s_at	SLC28A3	681
OC3P.5726.C1_s_at	SLC5A1	682
OCADNP.7872_s_at	SLC5A1	683
OCSR2.10331_x_at	SNORD114-14	684
OCSR2.8538_x_at	SNORD114-14	685
OCSR2.10331_at	SNORD114-14	686
OC3SNGn.2110-23a_s_at	SOX11	687
OCHP.1171_s_at	SOX11	688
OCHP.1523_s_at	SOX11	689
OC3SNGnh.19157_x_at	SPARC	690
OCHP.508_s_t	SPARC	691
OC3P.148.CB1-990a_s_at	SPARC	692
OCEM.2143_at	SPARC	693
OC3SNG.2614-40a_s_at	SPARC	694
OC3P.148.CB1_x_at	SPARC	695
OCEM.2143_x_at	SPARC	696
OC3SNG.1657-20a_s_at	SRPX	697
ADXGoodB4_at	TAP1	N/A
OC3SNG.2665-23a_s_at	TAP1	698
OC3P.5602.C1_s_at	TAP2	699
OCADNP.2260_s_at	TAP2	700
OCADNP.8242_s_at	TAP2	701
OC3SNGnh.18127_s_at	TAP2	702
OC3P.14195.C1_s_at	TIMP2	703
OCHP.320_s_at	TIMP2	704

TABLE 4-continued

Probeset	Gene	SEQ ID No.
OC3P.543.CB1_x_at	TIMP2	705
OC3SNGnh.19238_s_at	TIMP2	706
OC3P.543.CB1-699a_s_at	TIMP2	707
OCADNP.14191_s_at	TIMP2	708
OCADNP.13017_s_at	TIMP3	709
OCADA.9324_s_at	TIMP3	710
OCHP.1200_s_at	TIMP3	711
ADXGood73_s_at	TIMP3	N/A
OC3P.10470.C1_s_at	TIMP3	712
OC3P.15327.C1_s_at	TIMP3	713
OCHP.112_s_at	TIMP3	714
OC3P.5348.C1_s_at	TMEM45A	715
OC3P.4028.C1_at	TNFRSF14	716
OC3SNGn.2230-103a_s_at	TNFRSF14	717
OC3P.4028.C1_x_at	TNFRSF14	718
OC3SNG.1683-90a_s_at	TNFSF10	719
OC3P.2087.C1_s_at	TNFSF10	720
OCHP.318_x_at	TNFSF10	721
OC3SNGn.6279-343a_s_at	TNFSF10	722
OC3SNGn.5842-826a_x_at	TNFSF10	723
OCADNP.9180_s_at	TNFSF10	724
OCHP.1136_s_at	TUBA1A	725
OCADNP.7771_s_at	XAF1	726
ADXStrongB9_at	XAF1	N/A
OC3SNG.2606-619a_x_at	XAF1	727
OC3SNGnh.10895_s_at	XAF1	728
OC3P.4873.C1_s_at	XAF1	729
OC3SNGnh.10895_x_at	XAF1	730
OC3SNG.2605-236a_x_at	XAF1	731
OC3SNG.5460-81a_x_at	XAF1	732
OCADA.154_s_at	ZNF697	733
OCADA.3112_s_at	ZNF697	734

[0106] In one example embodiment, an expression signature comprises all or a portion of the following biomarkers; IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, RTP4, COL3A1, CDR1, RARRES3, TNFSF10, NUA1, SNORD114-14, SRPX, SPARC, GJB1, TIMP3, ISLR, TUBA1A, DEX1, BASP1, PXDN, GBP4, SLC28A3, HLA-DRA, TAP2, ACSL5, CDH11, PSMB9, MMP14, CD74, LOXL1, CIITA, ZNF697, SH3RF2, MIR198, COL1A2, TNFRSF14, COL8A1, C21orf63, TAP1, PDPN, RHOBTB3, BCL11A, HLA-DOB, XAF1, ARHGAP26, POLD2, DPYSL2, COL4A1, ID3, CFB, NID1, FKBP7, TIMP2, RCBTB1, ANGPTL2, ENTPD7, SHISA4, and HINT1,

[0107] In another example embodiment, an expression signature comprises IGF2, SOX11, INS, and CXCL17 and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0108] In another example embodiment, an expression signature comprises IGF2, INS, SPARC, TMEM45A, COL8A1 and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0109] In another example embodiment, an expression signature comprises IGF2, INS, SPARC, TMEM45A, COL8A1, COL3A1, CDR1, NUA1, TIMP3, LOXL1 and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7,

8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53.

[0110] In another example embodiment, an expression signature comprises IGF2, TIMP3, INS, CXCR2P1, NUA1 and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0111] In another example embodiment, an expression signature comprises IGF2, TIMP3, INS, CXCR2P1, NUA1, CDR1, MATN3, SOX11, SNORD114-14, COL3A1 and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53.

[0112] In another example embodiment, an expression signature comprises COL3A1, SPARC, CDR1, SRPX, MATN3 and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0113] In another example embodiment, an expression signature comprises COL3A1, SPARC, CDR1, SRPX, MATN3, TIMP3, CDH11, COL8A1, BCL11A, MMP14 and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53.

[0114] In another example embodiment, an expression signature comprises IGF2, CDR1, COL3A1, SPARC, TIMP3 and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0115] In another example embodiment, an expression signature comprises IGF2, CDR1, COL3A1, SPARC, TIMP3, INS, COL8A1, NUA1, MATN3, TMEM45A and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0116] In another example embodiment, an expression signature comprises INS, SPARC, COL8A1, COL3A1, CDR1, NUA1, TIMP3, and MMP14 and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, or 55.

[0117] In another example embodiment, an expression signature comprises at least INS, SPARC, COL8A1, COL3A1, CDR1, NUA1, TIMP3, and MMP14. In another

[0130] In another example embodiment, an expression signature comprises CXCR2P1 and at least N additional biomarkers selected from the list of biomarkers in Table 2, and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0131] In another example embodiment, an expression signature comprises SRPX and at least N additional biomarkers selected from the list of biomarkers in Table 2, and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0132] In another example embodiment, an expression signature comprises CDH11 and at least N additional biomarkers selected from the list of biomarkers in Table 2, and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0133] In another example embodiment, an expression signature comprises BC11A and at least N additional biomarkers selected from the list of biomarkers in Table 2, and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0134] In another example embodiment, an expression signature comprises LOXL1 and at least N additional biomarkers selected from the list of biomarkers in Table 2, and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0135] In another example embodiment, an expression signature comprises MMP14 and at least N additional biomarkers selected from the list of biomarkers in Table 2, and at least N additional biomarkers selected from the list of biomarkers in Table 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0136] In another example embodiment, an example expression signature comprises the biomarkers and corresponding biomarker weighted values listed in Table 2. In another example embodiment, an example expression signature consists of the biomarkers and corresponding biomarker weighted values listed in Table 2. In another example embodiment, an example expression score comprises the biomarkers and rank listed in Table 3. In another example embodiment, an example expression signature consists of the biomarkers and corresponding ranks listed in Table 3.

[0137] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising all or a portion of the biomarkers listed in Table 2 or 3.

[0138] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising IGF2, SOX11, INS, and CXCL17 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0139] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising IGF2, INS, SPARC, TMEM45A, COL8A1, and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0140] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising IGF2, INS, SPARC, TMEM45A, COL8A1, COL3A1, CDR1, NUAK1, TIMP3, LOXL1 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53.

[0141] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising IGF2, TIMP3, INS, CXCR2P1, NUAK1 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0142] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising IGF2, TIMP3, INS, CXCR2P1, NUAK1, CDR1, MATN3, SOX11, SNORD114-14, COL3A1 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53.

[0143] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising COL3A1, SPARC, CDR1, SRPX, MATN3, and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0144] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising COL3A1, SPARC, CDR1, SRPX, MATN3, TIMP3, CDH11, COL8A1, BCL11A, MMP14 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53.

[0145] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising IGF2, CDR1, COL3A1, SPARC, TIMP3, and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

[0146] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising IGF2, CDR1, COL3A1, SPARC, TIMP3, INS, COL8A1, NUA1, MATN3, TMEM45A and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53.

[0147] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising INS, SPARC, COL8A1, COL3A1, CDR1, NUA1, TIMP3, and MMP14 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, or 55.

[0148] In another example embodiment, an biomarker panel comprises at least INS, SPARC, COL8A1, COL3A1, CDR1, NUA1, TIMP3, and MMP14. In another example embodiment, the biomarker panel comprises at least IGF2, CDR1, COL3A1, SPARC, TIMP3, INS, COL8A1, NUA1, MATN3, TMEM45A. In another example embodiment, the biomarker panel comprises at least IGF2, CDR1, COL3A1,

SPARC, TIMP3. In another example embodiment, the biomarker panel comprises at least, COL3A1, SPARC, CDR1, SRPX, MATN3, TIMP3, CDH11, COL8A1, BCL11A, MMP14. In another example embodiment, the biomarker panel comprises at least COL3A1, SPARC, CDR1, SRPX, MATN3. In another example embodiment, the biomarker panel comprises at least COL3A1, SPARC, CDR1, SRPX, MATN3. In another example embodiment, the biomarker panel comprises at least IGF2, TIMP3, INS, CXCR2P1, NUA1, CDR1, MATN3, SOX11, SNORD114-14, COL3A1. In another example embodiment, the biomarker panel comprises at least IGF2, TIMP3, INS, CXCR2P1, NUA1. In another example embodiment, the biomarker panel comprises at least IGF2, INS, SPARC, TMEM45A, COL8A1, COL3A1, CDR1, NUA1, TIMP3, LOXL1. In another example embodiment, the biomarker panel comprises at least IGF2, INS, SPARC, TMEM45A, COL8A1. In another example embodiment, the biomarker panel comprises at least IGF2, SOX11, INS, and CXCL17.

[0149] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising IGF2 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0150] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising SOX11 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0151] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising INS and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0152] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising CXCL17 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0165] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising SRPX and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0166] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising CDH11 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0167] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising BC11A and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0168] In a further aspect, the methods of the present invention comprise conducting an assay on a biological sample from an individual to determine the expression levels of one or more biomarkers in a biomarker panel, the biomarker panel comprising MMP14 and at least N additional biomarkers selected from the list of biomarkers in Table 2 or 3, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62.

[0169] Classifying New Test Samples Using an Expression Signature

[0170] To classify new test samples using an expression signature, such as those described above, the relative expression levels of one or more biomarkers in a cancer tissue are measured to form a test sample expression profile. In certain example embodiments, the test sample expression profile is summarized in the form of a compound decision score ("expression score") and compared to a threshold score that is mathematically derived from a training set of patient data. The score threshold is established with the purpose of maximizing the ability to separate a patient group into different groups based on characteristics such as, but not limited to, good/poor clinical prognosis. The patient training set data is preferably derived from cancer tissue samples

having been characterized by prognosis, likelihood of recurrence, long term survival, clinical outcome, treatment response, diagnosis, cancer classification, or personalized genomics profile. Expression profiles, and corresponding decision scores from patient samples may be correlated with the characteristics of patient samples in the training set that are on the same side of the mathematically derived score decision threshold. In certain example embodiments, the threshold of the linear classifier scalar output is optimized to maximize the sum of sensitivity and specificity under cross-validation as observed within the training dataset.

[0171] The overall expression data for a given sample is normalized using methods known to those skilled in the art in order to correct for differing amounts of starting material, varying efficiencies of the extraction and amplification reactions, etc.

[0172] In one embodiment, the biomarker expression profile of a patient tissue sample is evaluated by a linear classifier. As used herein, a linear classifier refers to a weighted sum of the individual biomarker intensities into a compound decision score ("decision function"). The decision score is then compared to a pre-defined cut-off score threshold, corresponding to a certain set-point in terms of sensitivity and specificity which indicates if a sample is equal to or above the score threshold (decision function positive) or below (decision function negative).

[0173] Using a linear classifier on the normalized data to make a diagnostic or prognostic call (e.g. good or poor clinical prognosis) effectively means to split the data space, i.e. all possible combinations of expression values for all genes in the classifier, into two disjoint segments by means of a separating hyperplane. This split is empirically derived on a large set of training examples, for example from patients showing responsiveness or resistance to a therapeutic agent. Without loss of generality, one can assume a certain fixed set of values for all but one biomarker, which would automatically define a threshold value for this remaining biomarker where the decision would change from, for example, responsiveness or resistance to a therapeutic agent. Expression values above this dynamic threshold would then either indicate a poor clinical prognosis (for a biomarker with a negative weight) or a good clinical prognosis (for a biomarker with a positive weight). The precise value of this threshold depends on the actual measured expression profile of all other biomarkers within the classifier, but the general indication of certain biomarkers remains fixed, i.e. high values or "relative over-expression" always contributes to either a good clinical prognosis (genes with a positive weight) or a poor clinical prognosis (genes with a negative weights). Therefore, in the context of the overall gene expression classifier, relative expression can indicate if either up- or down-regulation of a certain biomarker is indicative of a good or bad clinical prognosis. In certain example embodiments, a sample expression score above the threshold expression score indicates the subject has the non-angiogenesis subtype. In certain other example embodiments, a sample expression score above a threshold score indicates the subject has a good clinical prognosis compared to a subject with a sample expression score below the threshold score. In certain other example embodiments, a sample expression score above the threshold score indicates the subject will likely experience a detrimental effect, or have a poor prognosis, if an anti-angiogenic therapeutic agent is administered.

[0174] There are a number of suitable methods for measuring expression profiles of test samples depending on the type of biomarker to be assayed. Measuring mRNA in a biological sample may be used as a surrogate for detection of the level of the corresponding protein in the biological sample. Thus, any of the biomarkers or biomarker panels described herein can also be detected by detecting the appropriate RNA. Methods of gene expression profiling include, but are not limited to, microarray, RT-PCT, qPCR, NGS, northern blots, SAGE, mass spectrometry.

[0175] mRNA expression levels are measured by reverse transcription quantitative polymerase chain reaction (RT-PCR followed with qPCR). RT-PCR is used to create a cDNA from the mRNA. The cDNA may be used in a qPCR assay to produce fluorescence as the DNA amplification process progresses. By comparison to a standard curve, qPCR can produce an absolute measurement such as number of copies of mRNA per cell. Northern blots, microarrays, Invader assays, and RT-PCR combined with capillary electrophoresis have all been used to measure expression levels of mRNA in a sample. See *Gene Expression Profiling: Methods and Protocols*, Richard A. Shimkets, editor, Humana Press, 2004.

[0176] miRNA molecules are small RNAs that are non-coding but may regulate gene expression. Any of the methods suited to the measurement of mRNA expression levels can also be used for the corresponding miRNA. Recently many laboratories have investigated the use of miRNAs as biomarkers for disease. Many diseases involve widespread transcriptional regulation, and it is not surprising that miRNAs might find a role as biomarkers. The connection between miRNA concentrations and disease is often even less clear than the connections between protein levels and disease, yet the value of miRNA biomarkers might be substantial. Of course, as with any RNA expressed differentially during disease, the problems facing the development of an in vitro diagnostic product will include the requirement that the miRNAs survive in the diseased cell and are easily extracted for analysis, or that the miRNAs are released into blood or other matrices where they must survive long enough to be measured. Protein biomarkers have similar requirements, although many potential protein biomarkers are secreted intentionally at the site of pathology and function, during disease, in a paracrine fashion. Many potential protein biomarkers are designed to function outside the cells within which those proteins are synthesized.

[0177] Gene expression may also be evaluated using mass spectrometry methods. A variety of configurations of mass spectrometers can be used to detect biomarker values. Several types of mass spectrometers are available or can be produced with various configurations. In general, a mass spectrometer has the following major components: a sample inlet, an ion source, a mass analyzer, a detector, a vacuum system, and instrument-control system, and a data system. Difference in the sample inlet, ion source, and mass analyzer generally define the type of instrument and its capabilities. For example, an inlet can be a capillary-column liquid chromatography source or can be a direct probe or stage such as used in matrix-assisted laser desorption. Common ion sources are, for example, electrospray, including nanospray and microspray or matrix-assisted laser desorption. Common mass analyzers include a quadrupole mass filter, ion trap mass analyzer and time-of-flight mass analyzer. Additional mass spectrometry methods are well known in

the art (see Burlingame et al., *Anal. Chem.* 70:647 R-716R (1998); Kinter and Sherman, New York (2000)).

[0178] Protein biomarkers and biomarker values can be detected and measured by any of the following: electrospray ionization mass spectrometry (ESI-MS), ESI-MS/MS, ESI-MS/(MS)_n, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS), desorption/ionization on silicon (DIOS), secondary ion mass spectrometry (SIMS), quadrupole time-of-flight (Q-TOF), tandem time-of-flight (TOF/TOF) technology, called ultraflex III TOF/TOF, atmospheric pressure chemical ionization mass spectrometry (APCI-MS), APCI-MS/MS, APCI-(MS).sup.N, atmospheric pressure photoionization mass spectrometry (APPI-MS), APPI-MS/MS, and APPI-(MS).sup.N, quadrupole mass spectrometry, Fourier transform mass spectrometry (FTMS), quantitative mass spectrometry, and ion trap mass spectrometry.

[0179] Sample preparation strategies are used to label and enrich samples before mass spectroscopic characterization of protein biomarkers and determination biomarker values. Labeling methods include but are not limited to isobaric tag for relative and absolute quantitation (iTRAQ) and stable isotope labeling with amino acids in cell culture (SILAC). Capture reagents used to selectively enrich samples for candidate biomarker proteins prior to mass spectroscopic analysis include but are not limited to aptamers, antibodies, nucleic acid probes, chimeras, small molecules, an F(ab')₂ fragment, a single chain antibody fragment, an Fv fragment, a single chain Fv fragment, a nucleic acid, a lectin, a ligand-binding receptor, affibodies, nanobodies, ankyrins, domain antibodies, alternative antibody scaffolds (e.g. diabodies etc) imprinted polymers, avimers, peptidomimetics, peptoids, peptide nucleic acids, threose nucleic acid, a hormone receptor, a cytokine receptor, and synthetic receptors, and modifications and fragments of these.

[0180] The foregoing assays enable the detection of biomarker values that are useful in methods for determining a patient's clinical prognosis and selecting appropriate treatment regimens, where the methods comprise detecting, in a biological sample from an individual, at least N biomarker values that each correspond to a biomarker selected from the group consisting of the biomarkers provided in Tables 1 or Table 2, wherein a classification, as described in detail below, using the biomarker values indicates whether the individual has a good prognosis or a bad prognosis, or will receive a detrimental or beneficial effect if a certain therapeutic agent is administered. While some of the described predictive biomarkers are useful alone for predicting clinical prognosis, methods are also described herein for the grouping of multiple subsets of the biomarkers that are each useful as a panel of two or more biomarkers. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least three biomarkers. It will be appreciated that N can be selected to be any number from any of the above-described ranges, as well as similar, but higher order, ranges. In accordance with any of the methods described herein, biomarker values can be detected and classified individually or they can be detected and classified collectively, as for example in a multiplex assay format.

[0181] b) Microarray Methods

[0182] In one embodiment, the present invention makes use of “oligonucleotide arrays” (also called herein “microarrays”). Microarrays can be employed for analyzing the expression of biomarkers in a cell, and especially for measuring the expression of biomarkers of cancer tissues.

[0183] In one embodiment, biomarker arrays are produced by hybridizing detectably labeled polynucleotides representing the mRNA transcripts present in a cell (e.g., fluorescently-labeled cDNA synthesized from total cell mRNA or labeled cRNA) to a microarray. A microarray is a surface with an ordered array of binding (e.g., hybridization) sites for products of many of the genes in the genome of a cell or organism, preferably most or almost all of the genes. Microarrays can be made in a number of ways known in the art. However produced, microarrays share certain characteristics. The arrays are reproducible, allowing multiple copies of a given array to be produced and easily compared with each other. Preferably the microarrays are small, usually smaller than 5 cm², and they are made from materials that are stable under binding (e.g., nucleic acid hybridization) conditions. A given binding site or unique set of binding sites in the microarray will specifically bind the product of a single gene in the cell. In a specific embodiment, positionally addressable arrays containing affixed nucleic acids of known sequence at each location are used.

[0184] It will be appreciated that when cDNA complementary to the RNA of a cell is made and hybridized to a microarray under suitable hybridization conditions, the level of hybridization to the site in the array corresponding to any particular gene will reflect the prevalence in the cell of mRNA transcribed from that gene/biomarker. For example, when detectably labeled (e.g., with a fluorophore) cDNA or cRNA complementary to the total cellular mRNA is hybridized to a microarray, the site on the array corresponding to a gene (i.e., capable of specifically binding the product of the gene) that is not transcribed in the cell will have little or no signal (e.g., fluorescent signal), and a gene for which the encoded mRNA is prevalent will have a relatively strong signal. Nucleic acid hybridization and wash conditions are chosen so that the probe “specifically binds” or “specifically hybridizes” to a specific array site, i.e., the probe hybridizes, duplexes or binds to a sequence array site with a complementary nucleic acid sequence but does not hybridize to a site with a non-complementary nucleic acid sequence. As used herein, one polynucleotide sequence is considered complementary to another when, if the shorter of the polynucleotides is less than or equal to 25 bases, there are no mismatches using standard base-pairing rules or, if the shorter of the polynucleotides is longer than 25 bases, there is no more than a 5% mismatch. Preferably, the polynucleotides are perfectly complementary (no mismatches). It can be demonstrated that specific hybridization conditions result in specific hybridization by carrying out a hybridization assay including negative controls using routine experimentation.

[0185] Optimal hybridization conditions will depend on the length (e.g., oligomer vs. polynucleotide greater than 200 bases) and type (e.g., RNA, DNA, PNA) of labeled probe and immobilized polynucleotide or oligonucleotide. General parameters for specific (i.e., stringent) hybridization conditions for nucleic acids are described in Sambrook et al., supra, and in Ausubel et al., “Current Protocols in Molecular Biology”, Greene Publishing and Wiley-interscience, NY

(1987), which is incorporated in its entirety for all purposes. When the cDNA microarrays are used, typical hybridization conditions are hybridization in 5×SSC plus 0.2% SDS at 65°C for 4 hours followed by washes at 25°C. in low stringency wash buffer (1×SSC plus 0.2% SDS) followed by 10 minutes at 25°C. in high stringency wash buffer (0.1×SSC plus 0.2% SDS) (see Shena et al., Proc. Natl. Acad. Sci. USA, Vol. 93, p. 10614 (1996)). Useful hybridization conditions are also provided in, e.g., Tijessen, Hybridization With Nucleic Acid Probes”, Elsevier Science Publishers B.V. (1993) and Kricka, “Nonisotopic DNA Probe Techniques”, Academic Press, San Diego, Calif. (1992).

[0186] c) Immunoassay Methods

[0187] Immunoassay methods are based on the reaction of an antibody to its corresponding target or analyte and can detect the analyte in a sample depending on the specific assay format. To improve specificity and sensitivity of an assay method based on immunoreactivity, monoclonal antibodies are often used because of their specific epitope recognition. Polyclonal antibodies have also been successfully used in various immunoassays because of their increased affinity for the target as compared to monoclonal antibodies. Immunoassays have been designed for use with a wide range of biological sample matrices. Immunoassay formats have been designed to provide qualitative, semi-quantitative, and quantitative results.

[0188] Quantitative results may be generated through the use of a standard curve created with known concentrations of the specific analyte to be detected. The response or signal from an unknown sample is plotted onto the standard curve, and a quantity or value corresponding to the target in the unknown sample is established.

[0189] Numerous immunoassay formats have been designed. ELISA or EIA can be quantitative for the detection of an analyte/biomarker. This method relies on attachment of a label to either the analyte or the antibody and the label component includes, either directly or indirectly, an enzyme. ELISA tests may be formatted for direct, indirect, competitive, or sandwich detection of the analyte. Other methods rely on labels such as, for example, radioisotopes (¹²⁵I) or fluorescence. Additional techniques include, for example, agglutination, nephelometry, turbidimetry, Western blot, immunoprecipitation, immunocytochemistry, immunohistochemistry, flow cytometry, Luminex assay, and others (see ImmunoAssay: A Practical Guide, edited by Brian Law, published by Taylor & Francis, Ltd., 2005 edition).

[0190] Example assay formats include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, fluorescent, chemiluminescence, and fluorescence resonance energy transfer (FRET) or time resolved-FRET (TR-FRET) immunoassays. Examples of procedures for detecting biomarkers include biomarker immunoprecipitation followed by quantitative methods that allow size and peptide level discrimination, such as gel electrophoresis, capillary electrophoresis, planar electrochromatography, and the like.

[0191] Methods of detecting and/or quantifying a detectable label or signal generating material depend on the nature of the label. The products of reactions catalyzed by appropriate enzymes (where the detectable label is an enzyme; see above) can be, without limitation, fluorescent, luminescent, or radioactive or they may absorb visible or ultraviolet light. Examples of detectors suitable for detecting such detectable labels include, without limitation, x-ray film, radioactivity counters, scintillation counters, spectrophotometers, colorimeters, fluorometers, luminometers, and densitometers.

[0192] Any of the methods for detection can be performed in any format that allows for any suitable preparation, processing, and analysis of the reactions. This can be, for example, in multi-well assay plates (e.g., 96 wells or 384 wells) or using any suitable array or microarray. Stock solutions for various agents can be made manually or robotically, and all subsequent pipetting, diluting, mixing, distribution, washing, incubating, sample readout, data collection and analysis can be done robotically using commercially available analysis software, robotics, and detection instrumentation capable of detecting a detectable label.

Kits

[0193] Reagents, tools, and/or instructions for performing the methods described herein can be provided in a kit. For example, the kit can contain reagents, tools, and instructions for determining an appropriate therapy for a cancer patient. Such a kit can include reagents for collecting a tissue sample from a patient, such as by biopsy, and reagents for processing the tissue. The kit can also include one or more reagents for performing a gene or gene product expression analysis, such as reagents for performing nucleic acid amplification (e.g. RT-PCR, qPCR), sequencing (e.g. next generation sequencing), northern blot, proteomic analysis, or immunohistochemistry to determine expression levels of gene or gene product markers in a sample of a patient. For example, primers for performing RT-PCR, probes for performing northern blot analyses, and/or antibodies for performing proteomic analysis such as Western blot, immunohistochemistry and ELISA analyses can be included in such kits. Appropriate buffers for the assays can also be included. Detection reagents required for any of these assays can also be included. The appropriate reagents and methods are described in further detail below. The kits may include suitable primers and/or probes to detect the expression levels of at least one (up to all) of the biomarkers of in Table 2. Where expression is determined at the protein level the kit may contain binding reagents specific for the proteins of interest. The binding reagents may comprise antibodies to include all fragments and derivatives thereof. In the context of the various embodiments of the present invention the term “antibody” includes all immunoglobulins or immunoglobulin-like molecules with specific binding affinity for the relevant protein (including by way of example and without limitation, IgA, IgD, IgE, IgG and IgM, combinations thereof, and similar molecules produced during an immune response in any vertebrate, for example, in mammals such as humans, goats, rabbits and mice). Specific immunoglobulins useful in the various embodiments of the invention include IgG isotypes. The antibodies useful in the various embodiments of the invention may be monoclonal or polyclonal in origin, but are typically monoclonal antibodies. Antibodies may be human antibodies, non-human antibodies, or humanized versions of non-human antibodies, or chimeric antibodies. Various techniques for antibody humanization are well established and any suitable technique may be employed. The term “antibody” also refers to a polypeptide ligand comprising at least a light chain or heavy chain immunoglobulin variable region which specifically recognizes and binds an epitope of an antigen, and it extends to all antibody derivatives and fragments that retain the ability to specifically bind to the relevant protein. These derivatives and fragments may include Fab fragments, F(ab')₂ fragments, Fv fragments, single chain antibodies, single domain

antibodies, Fc fragments etc. The term antibody encompasses antibodies comprised of both heavy and light chains, but also heavy chain (only) antibodies (which may be derived from various species of cartilaginous fish or camellids). In specific embodiments, the antibodies may be engineered so as to be specific for more than protein, for example bi-specific to permit binding to two different target proteins as identified herein (see Tables 2).

[0194] In some embodiments, the kits may also contain the specific anti-angiogenic therapeutic agent to be administered in the event that the test predicts responsiveness. This agent may be provided in a form, such as a dosage form, that is tailored to the specific treatment. The kit may be provided with suitable instructions for administration according to an appropriate treatment regimen.

[0195] The kits featured herein can also include an instruction sheet describing how to perform the assays for measuring gene or gene product expression. The instruction sheet can also include instructions for how to determine a reference cohort, including how to determine expression levels of gene or gene product markers in the reference cohort and how to assemble the expression data to establish a reference for comparison to a test patient. The instruction sheet can also include instructions for assaying gene or gene product expression in a test patient and for comparing the expression level with the expression in the reference cohort to subsequently determine the appropriate chemotherapy for the test patient. Methods for determining the appropriate chemotherapy are described above and can be described in detail in the instruction sheet.

[0196] Informational material included in the kits can be descriptive, instructional, marketing or other material that relates to the methods described herein and/or the use of the reagents for the methods described herein. For example, the informational material of the kit can contain contact information, e.g., a physical address, email address, website, or telephone number, where a user of the kit can obtain substantive information about performing a gene expression analysis and interpreting the results, particularly as they apply to a human's likelihood of having a positive response to a specific therapeutic agent.

[0197] The kits featured herein can also contain software necessary to infer a patient's likelihood of having a positive response to a specific therapeutic agent from the gene product marker expression.

Therapeutic Agents

[0198] As described above, the methods described herein permit the classification of a patient as having a good or bad clinical prognosis prior to, upon or following administration of an anti-angiogenic therapeutic agent following, or in combination with, a chemotherapeutic treatment. Some current such anti-angiogenic therapeutics used to treat cancer include, but are not limited to, the following agents; VEGF pathway-targeted therapeutic agent, including multi-targeted pathway inhibitors (VEGF/PDGF/FGF/EGF/FLT-3/c-KIT), Angiopoietin-TIE2 pathway inhibitors, endogenous angiogenic inhibitors, immunomodulatory Agents. VEGF specific inhibitors include, but are not limited to, Bevacizumab (Avastin), Aflibercept (VEGF Trap), IMC-1121B (Ramucirumab). Multi-targeted pathway inhibitors include, but are not limited to, Imatinib (Gleevec), Sorafenib (Nexavar), Gefitinib (Iressa), Sunitinib (Sutent), Erlotinib, Tivozinib, Cediranib (Recentin), Pazopanib (Votrient),

BIBF 1120 (Vargatef), Dovitinib, Semaxanib (Sugen), Axitinib (AG013736), Vandetanib (Zactima), Nilotinib (Tasigna), Dasatinib (Sprycel), Vatalanib, Motesanib, ABT-869, TKI-258. Angiopoietin-TIE2 pathway inhibitors include, but are not limited to, AMG-386, PF-4856884 CVX-060, CEP-11981, CE-245677, MEDI-3617, CVX-241, Trastuzumab (Herceptin). Endogenous angiogenic inhibitors include, but are not limited to, Thrombospondin, Endostatin, Tumstatin, Canstatin, Arrestin, Angiostatin, Vasostatin, Interferon alpha. Immunomodulatory Agents include, but are not limited to, Thalidomide and Lenalidomide. In one example embodiment, the anti-angiogenic agent is bevacizumab.

[0199] The invention is further defined in the following numbered clauses:

[0200] 1. A method for selecting whether to administer an anti-angiogenic therapeutic agent to subjects, comprising:

[0201] obtaining a test sample from a subject;

[0202] measuring expression levels of a biomarker panel from the test sample obtained from the subject, wherein the biomarker panel comprises one or more biomarkers selected from Table 2 or Table 3;

[0203] determining a sample expression score for the biomarker panel;

[0204] comparing the sample expression score to a threshold score; and

[0205] selecting a treatment based on whether the sample expression score is above or equal to the threshold expression score, wherein if the sample expression score is above the threshold score an anti-angiogenic agent is contraindicated.

[0206] 2. The method of clause 1, wherein the subject is suffering from cancer.

[0207] 3. The method of clause 2, wherein the cancer is ovarian cancer.

[0208] 4. The method of clause 3, wherein the ovarian cancer is high grade serous ovarian cancer.

[0209] 5. The method of any one of clauses 1 to 4, wherein the subject is receiving or has received chemotherapeutic treatment.

[0210] 6. The method of clause 5, wherein the chemotherapeutic treatment comprises administration of a platinum-based chemotherapeutic agent, an alkylating agent, an anti-metabolite, an anti-tumor antibiotic, a topoisomerase inhibitor, a mitotic inhibitor, or a combination thereof.

[0211] 7. The method of clause 6, wherein the chemotherapeutic treatment comprises administration of a platinum based-chemotherapeutic agent, a mitotic inhibitor, or a combination thereof.

[0212] 8. The method of clause 6, wherein the chemotherapeutic treatment comprises administration of carboplatin and paclitaxel.

[0213] 9. The method of any one of clauses 1 to 8, wherein the anti-angiogenic therapeutic agent is a VEGF-pathway-targeted therapeutic agent, an angiopoietin-TIE2 pathway inhibitor, an endogenous angiogenic inhibitor, or an immunomodulatory agent.

[0214] 10. The method of clause 9, wherein the VEGF pathway-targeted therapeutic agents include Bevacizumab (Avastin), Afibercept (VEGF Trap), IMC-1121B (Ramucirumab), Imatinib (Gleevec), Sorafenib (Nexavar), Gefitinib (Iressa), Sunitinib (Sutent), Erlotinib, Tivozinib, Cediranib (Recentin), Pazopanib (Votrient), BIBF 1120 (Vargatef), Dovitinib, Semaxanib (Sugen), Axitinib (AG013736), Van-

detanib (Zactima), Nilotinib (Tasigna), Dasatinib (Sprycel), Vatalanib, Motesanib, ABT-869, TKI-258 or a combination thereof.

[0215] 11. The method of clause 16, wherein the angiopoietin-TIE2 pathway inhibitor includes AMG-386, PF-4856884 CVX-060, CEP-11981, CE-245677, MEDI-3617, CVX-241, Trastuzumab (Herceptin) or a combination thereof.

[0216] 12. The method of clause 9, wherein the endogenous angiogenic inhibitors include Thrombospondin, Endostatin, Tumstatin, Canstatin, Arrestin, Angiostatin, Vasostatin, Interferon alpha or a combination thereof.

[0217] 13. The method of clause 9, wherein the immunomodulatory agents include thalidomide and lenalidomide.

[0218] 14. The method of clause 10, wherein the VEGF pathway-targeted therapeutic agent is bevacizumab.

[0219] 15. The method of any one of clauses 1 to 14, wherein the biomarker panel comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.

[0220] 16. The method of any one of clauses 1 to 14, wherein the biomarker panel comprises the biomarkers listed in Table 2.

[0221] 17. The method of clause 16, wherein the expression score is calculated using a weight value and a bias value for each biomarker in the biomarker panel, and wherein the weight value and the bias value are defined for each biomarker in Table 2.

[0222] 18. The method of clause 16, wherein the expression score is calculated using a weight value for each biomarker in the biomarker panel, and wherein the weight for each biomarker is ranked in decreasing absolute value as defined in Table 3.

[0223] 19. The method of any one of clauses 1 to 14, wherein the biomarker panel comprises one or more of IGF2, CDR1, COL3A1, SPARC, TIMP3, INS, COL8A1, NUA1, MATN3, TMEM45A.

[0224] 20. The method of any one of clauses 1 to 14, wherein the biomarker panel comprises one or more INS, SPARC, COLA1, COL3A1, CDR1, NUA1, TIMP3, and MMP14.

[0225] 21. A method for determining clinical prognosis of subjects, comprising:

[0226] obtaining a test sample from a subject suffering from cancer;

[0227] measuring expression levels of a biomarker panel from the test sample obtained from the subject, wherein the biomarker panel comprises one or more biomarkers selected from Table 2;

[0228] determining a sample expression score for the biomarker panel;

[0229] comparing the sample expression score to a threshold score; and

[0230] determining a clinical prognosis for the subject based on whether the sample expression score is above the threshold expression score, wherein if the sample expression score is above or equal to the threshold expression score the clinical prognosis is a good prognosis.

[0231] 22. The method of clause 21, wherein the good prognosis indicates increased progression free survival or overall survival rates compared to samples with a sample expression score below the threshold score.

[0232] 23. The method of clause 21 or clause 22, wherein the cancer is ovarian cancer.

[0233] 24. The method of clause 23, wherein the ovarian cancer is high grade serous ovarian cancer.

[0234] 25. The method of any one of clauses 21 to 24, wherein the chemotherapeutic treatment comprises administration of a platinum-based chemotherapeutic agent, an alkylating agent, an anti-metabolite, an anti-tumor antibiotic, a topoisomerase inhibitor, a mitotic inhibitor, or a combination thereof.

[0235] 26. The method of clause 25, wherein the chemotherapeutic treatment comprises administration of a platinum-based chemotherapeutic agent, a mitotic inhibitor, or a combination thereof.

[0236] 27. The method of clause 25, wherein the chemotherapeutic treatment comprises administration of paclitaxel and carboplatin.

[0237] 28. The method of any one of clauses 21 to 27, wherein the biomarker panel comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.

[0238] 29. The method any one of clauses 21 to 28, wherein the biomarker panel comprises the biomarkers listed in Table 2.

[0239] 30. The method of clause 29, wherein the expression score is calculated using a weight value and a bias value for each biomarker in the biomarker panel, and wherein the weight value and bias value for each biomarker are defined in Table 2.

[0240] 31. The method of clause 29, wherein the expression score is calculated using a weight value for each biomarker in the biomarker panel, and wherein the weight for each biomarker is ranked in decreasing absolute value as defined in Table 3.

[0241] 32. The method of any one of clauses 21 to 28, wherein the biomarker panel comprises one or more of IGF2, CDR1, COL3A1, SPARC, TIMP3, INS, COL8A1, NUA1, MATN3, TMEM45A.

[0242] 33. The method of any one of clauses 21 to 28, wherein the biomarker panel comprises one or more INS, SPARC, COLA1, COL3A1, CDR1, NUA1, TIMP3, and MMP14.

[0243] 34. A method for selecting whether to administer Bevacizumab to a subject, comprising:

[0244] in a test sample obtained from a subject suffering from ovarian cancer, which subject is being, has been and/or will be treated using a platinum-based chemotherapeutic agent and/or a mitotic inhibitor;

[0245] measuring expression levels of one or more, up to all of the, biomarkers selected from Table 2;

[0246] determining a sample expression score for the one or more biomarkers;

[0247] comparing the sample expression score to a threshold score; and

[0248] selecting a treatment based on whether the sample expression score is above the threshold expression score, wherein if the sample expression score is above or equal to the threshold score Bevacizumab is contraindicated.

[0249] 35. The method of clause 34 wherein the ovarian cancer comprises serous ovarian cancer.

[0250] 36. The method of clause 35 wherein the serous ovarian cancer is high grade serous ovarian cancer.

[0251] 37. The method of any one of clauses 34 to 35 wherein if Bevacizumab is contraindicated the patient is treated with a platinum-based chemotherapeutic agent and/or a mitotic inhibitor.

[0252] 38. The method of any one of clauses 34 to 37 wherein if the sample expression score is below the threshold score the patient is treated with a platinum-based chemotherapeutic agent and/or a mitotic inhibitor together with Bevacizumab.

[0253] 39. The method of any one of clauses 34 to 38, wherein the platinum-based chemotherapeutic agent comprises carboplatin.

[0254] 40. The method of any one of clauses 34 to 39, wherein the mitotic inhibitor comprises a taxane, optionally paclitaxel.

[0255] 41. The method of any one of clauses 34 to 40, wherein the biomarker panel comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.

[0256] 42. The method any one of clauses 34 to 40, wherein the biomarker panel comprises the biomarkers listed in Table 2.

[0257] 43. The method of clause 42, wherein the expression score is calculated using a weight value and a bias value for each biomarker in the biomarker panel, and wherein the weight value and bias value for each biomarker are defined in Table 2.

[0258] 44. The method of clause 42, wherein the expression score is calculated using a weight value for each biomarker in the biomarker panel, and wherein the weight for each biomarker is ranked in decreasing absolute value as defined in Table 3.

[0259] 45. The method of any one of clauses 34 to 40, wherein the biomarker panel comprises one or more of IGF2, CDR1, COL3A1, SPARC, TIMP3, INS, COL8A1, NUA1, MATN3, TMEM45A.

[0260] 46. The method of any one of clauses 34 to 40, wherein the biomarker panel comprises one or more INS, SPARC, COLA1, COL3A1, CDR1, NUA1, TIMP3, and MMP14.

[0261] 47. A method for determining clinical prognosis of a subject, comprising:

[0262] a. in a test sample obtained from a subject suffering from ovarian cancer, which subject is being, has been and/or will be treated using a platinum-based chemotherapeutic agent and/or a mitotic inhibitor;

[0263] b. measuring expression levels of one or more, up to all of the, biomarkers selected from Table 2;

[0264] c. determining a sample expression score for the one or more biomarkers;

[0265] d. comparing the sample expression score to a threshold score; and

[0266] e. determining the clinical prognosis based on whether the sample expression score is above or equal to the threshold expression score, wherein if the sample expression score is above or equal to the threshold score the clinical prognosis is a good clinical prognosis.

[0267] 48. The method of clause 47, wherein the ovarian cancer comprises serous ovarian cancer.

[0268] 49. The method of clause 48, wherein the serous ovarian cancer is high grade serous ovarian cancer.

[0269] 50. The method of any one of clauses 47 to 48, wherein if the patient has a good prognosis, treatment using Bevacizumab is contraindicated.

[0270] 51. The method of any one of clauses 47 to 50 wherein if the sample expression score is below the thresh-

old score the patient is treated with a platinum-based chemotherapeutic agent and/or a mitotic inhibitor together with Bevacizumab.

[0271] 52. The method of any one of clauses 47 to 51, wherein the platinum-based chemotherapeutic agent comprises carboplatin.

[0272] 53. The method of any one of clauses 47 to 52, wherein the mitotic inhibitor comprises a taxane, optionally paclitaxel.

[0273] 54. The method of any one of clauses 47 to 53, wherein the biomarker panel comprises one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.

[0274] 55. The method any one of clauses 47 to 53, wherein the biomarker panel comprises the biomarkers listed in Table 2.

[0275] 56. The method of clause 55, wherein the expression score is calculated using a weight value and a bias value for each biomarker in the biomarker panel, and wherein the weight value and bias value for each biomarker are defined in Table 2.

[0276] 57. The method of clause 55, wherein the expression score is calculated using a weight value for each biomarker in the biomarker panel, and wherein the weight for each biomarker is ranked in decreasing absolute value as defined in Table 3.

[0277] 58. The method of any one of clauses 47 to 52, wherein the biomarker panel comprises one or more of

IGF2, CDR1, COL3A1, SPARC, TIMP3, INS, COL8A1, NUA1, MATN3, TMEM45A.

[0278] 59. The method of any one of clauses 47 to 52, wherein the biomarker panel comprises one or more INS, SPARC, COLA1, COL3A1, CDR1, NUA1, TIMP3, and MMP14.

[0279] This invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications, and equivalents thereof which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or scope of the appended claims.

EXAMPLES

Example 1

Tissue Processing, Hierarchical Clustering, Subtype Identification and Classifier Development

Tumor Material

[0280] Example expression signatures were identified from gene expression analysis of a cohort of macrodissected epithelial serous ovarian tumor FFPE tissue samples sourced from the NHS Lothian and University of Edinburgh.

TABLE 3

results of pathology review of 357 epithelial ovarian cancer samples.												
	All patients (N = 357)		Cluster A (N = 106)		Cluster B (N = 97)		Cluster C (N = 79)		Cluster D (N = 75)		unadjusted	p-value
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	p-value	(corrected)
Age at diagnosis, yrs												
Median	60.6		60.4		60.6		63.7		57.8		0.004	0.13
Range	23-86		36-83		30-86		33-84		23-78			
Block age, yrs												
Median	8.7		8.5		9.0		8.7		8.3		0.73	1.00
Range	2.9-24.1		2.9-24.1		3.0-22.2		2.9-19.5		2.9-19.4			
Histology												
High grade serous	265	(74)	96	(91)	86	(89)	72	(91)	11	(15)	3.66×10^{-33}	1.24×10^{-31}
Low grade serous	12	(3)	0	(0)	4	(4)	1	(1)	7	(9)		
Endometrioid	45	(13)	6	(6)	4	(4)	4	(5)	31	(41)		
Clear cell	26	(7)	4	(4)	3	(3)	2	(3)	17	(23)		
Mucinous	9	(3)	0	(0)	0	(0)	0	(0)	9	(12)		
Grade*												
High	300	(84)	103	(97)	91	(94)	76	(96)	30	(40)	1.21×10^{-29}	4.12×10^{-28}
Low	57	(16)	3	(3)	6	(6)	3	(4)	45	(60)		
FIGO stage												
I	46	(13)	6	(6)	1	(1)	7	(9)	32	(43)	2.71×10^{-18}	9.20×10^{-17}
II	41	(11)	11	(10)	6	(6)	5	(6)	19	(25)		
III	206	(58)	67	(63)	72	(74)	51	(65)	16	(21)		
IV	55	(15)	19	(18)	15	(15)	15	(19)	6	(8)		
Inadequate info	9	(3)	3	(3)	3	(3)	1	(1)	2	(3)		
Debulking**												
<2 cm	166	(46)	41	(39)	34	(35)	34	(43)	57	(76)	1.69×10^{-6}	5.75×10^{-5}
2-5 cm	68	(19)	22	(21)	20	(21)	21	(27)	5	(7)		
>5 cm	84	(24)	25	(24)	31	(32)	21	(27)	7	(9)		
Unknown	39	(11)	18	(17)	12	(12)	3	(4)	6	(8)		

TABLE 3-continued

results of pathology review of 357 epithelial ovarian cancer samples.												
	All patients (N = 357)		Cluster A (N = 106)		Cluster B (N = 97)		Cluster C (N = 79)		Cluster D (N = 75)		unadjusted	p-value
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	p-value	(corrected)
1 st line chemotherapy												
Platinum alone	218	(61)	57	(54)	60	(62)	51	(65)	50	(67)	0.70	1.00
Platinum plus taxane	128	(36)	45	(42)	34	(35)	26	(33)	23	(31)		
Other	11	(3)	4	(4)	3	(3)	2	(3)	2	(3)		
Relapse												
Recurrence	276	(77)	88	(83)	87	(90)	69	(87)	32	(43)	2.65×10^{-14}	9.02×10^{-13}
Did not recur	81	(23)	18	(17)	10	(10)	10	(13)	43	(57)		

Gene Expression Profiling from FFPE

[0281] Total RNA was extracted from macrodissected FFPE tissue using the High Pure RNA Paraffin Kit (Roche Diagnostics GmbH, Mannheim, Germany). RNA was converted into complementary deoxyribonucleic acid (cDNA), which was subsequently amplified and converted into single-stranded form using the SPLA® technology of the WT-Ovation™ FFPE RNA Amplification System V2 (NuGEN Technologies Inc., San Carlos, Calif., USA). The amplified single-stranded cDNA was then fragmented and biotin labeled using the FL-Ovation™ cDNA Biotin Module V2 (NuGEN Technologies Inc.). The fragmented and labeled cDNA was then hybridized to the Almac Ovarian Cancer DSA™. Almac's Ovarian Cancer DSA™ research tool has been optimised for analysis of FFPE tissue samples, enabling the use of valuable archived tissue banks. The Almac Ovarian Cancer DSA™ research tool is an innovative microarray platform that represents the transcriptome in both normal and cancerous ovarian tissues. Consequently, the Ovarian Cancer DSA™ provides a comprehensive representation of the transcriptome within the ovarian disease and tissue setting, not available using generic microarray platforms. Arrays were scanned using the Affymetrix Genechip® Scanner 7G (Affymetrix Inc., Santa Clara, Calif.).

Data Preparation

[0282] Quality Control (QC) of profiled samples was carried out using MASS pre-processing algorithm. Different technical aspects were addressed: average noise and background homogeneity, percentage of present call (array quality), signal quality, RNA quality and hybridization quality. Distributions and Median Absolute Deviation of corresponding parameters were analyzed and used to identify possible outliers.

[0283] Almac's Ovarian Cancer DSA™ contains probes that primarily target the area within 300 nucleotides from the 3' end. Therefore standard Affymetrix RNA quality measures were adapted—for housekeeping genes intensities of 3' end probe sets with ratios of 3' end probe set intensity to the average background intensity were used in addition to usual 3'/5' ratios. Hybridization controls were checked to ensure that their intensities and present calls conform to the requirements specified by Affymetrix.

Hierarchical Clustering and Functional Analysis

[0284] Sample pre-processing was carried out using Robust Multi-array Average (RMA) [16]. The data matrix

was sorted by decreasing variance, decreasing intensity and increasing correlation to cDNA yield. Following filtering of probe sets correlated with cDNA yield, incremental subsets of the data matrix were tested for cluster stability: the GAP statistic [17] was applied to calculate the number of sample and probe set clusters while the stability of cluster composition was assessed using partition comparison methods [18, 19]. The final most variable probe set list was determined based on the smallest and most stable data matrix for the selected number of sample cluster.

[0285] Following standardization of the data matrix to the median probe set expression values, agglomerative hierarchical clustering was performed using Euclidean distance and Ward's linkage method [20]. The optimal number of sample and probe set clusters was determined using the GAP statistic [17]. The significance of the distribution of clinical parameter factor levels across sample clusters was assessed using ANOVA (continuous factor) or chi-squared analysis (discrete factor) and corrected for false discovery rate (product of p-value and number of tests performed). A corrected p-value threshold of 0.05 was used as criterion for significance.

[0286] Ovarian Cancer DSA® probe sets were remapped to genes using an annotation pipeline based on Ensembl v60 [http://oct2012.archive.ensembl.org/]. Functional enrichment analysis was conducted to identify and rank biological entities which were found to be associated with the clustered gene sets using the Gene Ontology biological processes classification [21]. Entities were ranked according to a statistically derived enrichment score [22] and adjusted for multiple testing [23]. A corrected p-value of 0.05 was used as significance threshold. The identified enriched processes were summarised into an overall group function for each probe set/gene cluster.

Signature Development and Evaluation

[0287] Following subtype identification, a gene signature was developed for predicting the molecular group. To facilitate application of a signature to samples profiled on different platforms, probe sets were remapped to genes by summarizing all probe sets to their median expression and log 2 transforming the data. Signature generation was performed using the partial least squares method [24] with the selection of features/genes based on filter feature selection during 10 repeats of five-fold cross-validation.

[0288] Univariate and multivariable survival analysis was performed using the survival package [25] in R 2.15.0. Multivariable analysis corrected for the following factors:

High grade serous: Debulking status, Stage, Chemotherapy and Age at diagnosis; Tothill: Grade, Stage, Neoadjuvant treatment and Residual disease. All Kaplan-Meier graphs are a univariate representation of survival data.

Results

[0289] 265 HGS tumors underwent unsupervised hierarchical clustering based on 1400 most variable probe sets (corresponding to 1040 genes). Three sample clusters and four gene clusters were identified (FIG. 1). There was no significant association between HGS clusters and clinico-pathological features. Functional analysis (FIG. 1) revealed that cluster HGS3 was characterized by up regulation of genes associated with immune response and angiogenesis/vascular development (cluster referred to as Angioimmune forthwith). Cluster HGS1 was associated with upregulation of angiogenesis/vascular development (although apparently to a lesser extent than cluster HGS3) but without high expression of genes involved in immune response (cluster referred to as Angio forthwith). Cluster HGS2 was characterized by upregulation of genes involved in immune response without upregulation of genes involved in angiogenesis or vascular development (cluster referred to as Immune forthwith).

[0290] Multivariable survival analysis according to subgroup revealed that the patients in the Immune cluster had significantly prolonged OS compared to both patients in the Angioimmune (HR=0.58 [0.41-0.82], p_{adj} =0.001) and Angio clusters (HR=0.55 [0.37-0.80], p_{adj} =0.001). Kaplan-Meier curves are shown in FIG. 2 (univariable HR and p-values are shown).

[0291] Since patients in the Immune cluster had a significantly better outcome than those in the other clusters we proceeded to develop an assay to prospectively identify these patients in the clinic. In addition, given the low expression of angiogenic genes in the immune cluster, we hypothesized that this assay may identify a population that would not benefit from therapies targeting angiogenesis, although it would require additional datasets to test this theory. For the purpose of signature generation the Angio and Angioimmune clusters were grouped together and labeled as the “pro-angiogenic” group.

[0292] A 63-gene biomarker assay was then developed that could identify patients in the immune cluster (Table 2). Consistent with the hierarchical clustering analysis, patients classified by the assay as being in the Immune cluster had a significantly improved progression free survival (PFS) (multivariable analysis; HR=0.72 [0.52-0.99], p =0.043) and OS (multivariable analysis; HR=0.61 [0.44-0.86], p =0.004) compared to the other HGS patients. These multivariate analyses corrected for debulking status, stage, chemotherapy and age at diagnosis. Kaplan-Meier curves for PFS and OS according to signature call in the Edinburgh dataset are shown in FIGS. 3A and 3B respectively with univariate HR performance displayed on each figure.

[0293] In order to independently validate our biomarker as a prognostic assay, it was applied to the HGS ovarian tumors within the dataset of Tothill et al. Clinical Cancer Research 2008; 14(16):5198-208. The patients identified as being in the Immune cluster had a significantly improved PFS (multivariable analysis; HR=0.62 [0.41-0.95], p =0.029) and OS (multivariable analysis; HR=0.32 [0.19-0.54], p =0.00001) compared to the other HGS patients. These multivariate analyses corrected for grade, stage, neoadjuvant treatment

and residual disease. Kaplan-Meier curves for PFS and OS according to signature call in the Tothill dataset are shown in FIGS. 4A and 4B respectively, with univariate HR performance displayed on each figure.

Example 2

Independent Validation of the Predictive Utility of the “Immune” Signature

Background

[0294] The International Collaboration on Ovarian Neoplasms 7 (ICON7) trial is a Gynecologic Cancer Intergroup phase 3 trial that assessed the effects of adding bevacizumab, concurrently and as a continuation, to standard chemotherapy with carboplatin and paclitaxel in patients with primary peritoneal carcinoma, fallopian tube carcinoma, and epithelial ovarian carcinoma (Perren T J, Swart A M, Pfisterer J, Ledermann J A, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 365(26): 2484-96, Aghajanian C, Blank S V, Goff B A, Judson P L, Teneriello M G, Husain A, et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *Journal of Clinical Oncology.* 2012; 30(17): 2039-45).

[0295] Patient characteristics, progression-free survival, toxicity, and preliminary overall survival data and a summary of quality-of-life (QoL) data have been reported from ICON7. In the standard chemotherapy group, 696 (91%) of 764 women received 18 weeks of chemotherapy by protocol. In the bevacizumab group, 719 (94%) of 764 women received 18 weeks of chemotherapy and bevacizumab and 472 (62%) continued bevacizumab to protocol completion at 54 weeks. The hazard ratio for progression-free survival with standard chemotherapy and bevacizumab was 0.81 (95% CI 0.70-0.94, p =0.004). In patients at high risk of progression, defined as International Federation of Gynecology and Obstetrics (FIGO) stage IV disease or stage III disease with greater than 1.0 cm of residual disease after debulking surgery, the hazard ratio for death in the bevacizumab group was 0.64 (95% CI 0.48-0.85; p =0.002).

Methods

[0296] Access was obtained to the ICON7 trial samples via the Medical Research Council (MRC). An honest broker held the associated clinical data from the MRC. A randomization strategy for profiling the samples has been performed based on clinical factors. All reagents, arrays, and reference samples were previously tested and passed qualification criteria.

[0297] To confirm diagnosis and histological type, all samples were independently reviewed using H+E slides by two specialist gynecological pathologists and WT1 staining was used to confirm serous histology in problematic cases. Sections were taken from FFPE blocks (almost exclusively from an adnexal mass rather than peritoneal or omental disease) and macrodissected under bright field microscopy to minimize stromal contamination (<10%). The number of 10 μ m sections used was dependent on the percentage of tumor in the block: two, three and four for >50%, 25-50% and <25% tumor content in the block respectively.

[0298] Total RNA was extracted from macrodissected FFPE tissue using the High Pure RNA Paraffin Kit (Roche Diagnostics GmbH, Mannheim, Germany). RNA was converted into complementary deoxyribonucleic acid (cDNA), which is subsequently amplified and converted into single-stranded form using the SPIA® technology of the WT-Ovation™ FFPE RNA Amplification System V2 (NuGEN Technologies Inc., San Carlos, Calif., USA). The amplified single-stranded cDNA is then fragmented and biotin labeled using the FL-Ovation™ cDNA Biotin Module V2 (NuGEN Technologies Inc.). The fragmented and labeled cDNA was then hybridized to the Almac Ovarian Cancer DSA, on this the signature was developed. Arrays are scanned using the Affymetrix Genechip® Scanner 7G (Affymetrix Inc., Santa Clara, Calif.).

[0299] After pathology review there were 286 patients in the sample with high grade serous ovarian cancer; 144 patients from the bevacizumab arm, and 142 from the no bevacizumab arm. It was estimated that 69% of patients would be in the pro-angiogenic patient group and that this would be the same in both study arms.

[0300] The primary study hypothesis was that within the 'pro-angiogenic' subgroup there will be a marked effect of bevacizumab, corresponding to at least halving of the hazard ratio for progression-free survival compared to the immune subgroup. By contrast the expectation is that in the 'immune' subgroup bevacizumab will have at best no effect or may even be slightly disadvantageous.

[0301] Five samples failed processing QC such that there were 238 progression-free survival events (83%) in high grade serous clinical study data set. The estimated study power (using formula 6 in C Schmoor, W Sauerbrei, and M Schumacher Sample size considerations for the evaluation of prognostic factors in survival analysis Statist. Med. 2000; 19:441-452) to detect $\theta > 2$ (corresponding to the differential effect of bevacizumab outlined in the previous paragraph) is 88% at the 10% one-sided level of statistical significance. There were 147 deaths in the data set and the power for the same analysis on survival was 75%.

[0302] Progression free survival was the primary end-point; this is the MRC calculated time provided in the data set. This is time from randomization to progression or death (from any cause) whichever occurs first. Overall survival was a secondary study end-point. This is time from randomization to death from any cause.

[0303] A stratified Cox-proportional hazards model was fitted to the progression-free survival data initially. The model had a single effect term for randomised study arm. A second stratified Cox-proportional hazards model was then fitted to the progression-free survival data. This model was also be stratified, but had separate terms for the effect of randomised study arm within each strata.

[0304] The log-likelihood of the two fitted models were compared to determine whether the effect of randomised study arm depends on pro-angiogenic status (chi-square test with degrees of freedom corresponding to number of strata-1). If the above test is statistically significant at the 5% level of statistical significance then the appropriateness of the proportional hazards assumption for the model with separate terms for randomised study arm within each strata would be assessed.

[0305] The test for proportional hazards was done via the Grambsch-Therneau test [P. Grambsch and T. Therneau (1994), Proportional hazards tests and diagnostics based on

weighted residuals. *Biometrika*, 81, 515-26]. Progression-free survival times were transformed to a log scale for the test. The tests on each of the terms for study arm within each strata were assessed separately using the 5% level of statistical significance. If the test for proportional hazard was rejected within one or more of the strata then a restricted mean survival model would be fitted within each strata using flexible parametric survival models [P Royston, M K B Parmar The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt Stat Med, 30 (2011), pp. 2409-2421]. These models would use 3 degrees of freedom to estimate the baseline distribution function and 1 degree of freedom for the time dependent treatment effect. The maximum time over which the restricted mean would be calculated in each case was 3 years.

[0306] The above analysis will be repeated for overall survival.

Results

[0307] For patients classified as in the immune subtype (39%), the addition of bevacizumab conferred a worse progression free survival (HR 1.73 (1.12-2.68)) and overall survival (HR 2.00 (1.11-3.61)) when compared to proangiogenic patients. See FIGS. 5A-B and 6A-B. Accordingly, subjects with the Immune cancer subtype exhibited a poor prognosis when bevacizumab was added to their treatment regimen compared to subjects that did not have the Immune cancer subtype.

Example 3

Independent Validation of the Prognostic Utility of Immune Signature

[0308] The primary objections of the study were: 1. prediction of individual risk of tumour recurrence using the 63-gene signature on patient's gene expression data; 2. evaluation of the performance of the signature prognostic prediction with regards to patients progressive free survival (PFS) outcome as well as overall survival (OS); 3. investigation of the influence of clinical covariates on the signature prognostic performance in relation to the progressive free survival event.

[0309] This exploratory study included all the 139 patients in the control arm of the study. It was estimated that 85 (61.2%) of the patients would be categorized as pro-angiogenic (signature negative) by the gene signature. The chart and follow-up review indicated that 72 had progression-free survival events, with 46 deaths (overall survival events) occurring in the arm (information on patient numbers and percentages were provided by Jim Paul).

[0310] A retrospective power calculation using a sample size and power calculation method (Freedman, L. S. (1982). Tables of the number of patients required in clinical trials using the log-rank test. *Statistics in Medicine*. 1: 121-129) under a Cox proportional hazards regression showed that the above study figures will provide approximately 85% power to detect an hazard ratio (HR) of 0.5 when comparing progression free survival of 'immune only' with 'pro-angiogenic' molecular subgroups patients at 2-sided 5% level of significance.

[0311] Time to event (survival) analysis using the progression free survival as outcome was performed to evaluate the

prognostic effects of the signature. The survival distributions of patient groups defined by the angiogenic status ('pro-angiogenic or signature negative' and 'immune-only or signature positive') were visualized using the Kaplan-Meier (KM) curve.

[0312] The Cox proportional hazards regression was performed to relate the patients' angiogenic status (negative or positive) to progression free survival event. In addition to the univariate (unadjusted) exploration, the multivariable (adjusted) Cox model was performed to explore the effect of the signature molecular subgroups (positive or negative) on the PFS and OS adjusting for other important clinical covariates. All estimated effects were reported with 95% confidence intervals from an analysis in which the signature and standard prognostic variables are included, regardless of their significance (P Royston, MKB Parmar The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt Stat Med, 30 (2011), pp. 2409-2421). Due to size limitation only a few important covariates were considered; these included FIGO stage, tumour grade, debulking status, performance status (ECOG) and patient age.

[0313] The appropriateness of the proportional hazards assumption across the molecular subgroup was investigated before interpreting the Cox model results. In line with the previous analysis of study trial data, a restricted mean survival model was fitted for each molecular subgroup If the test for proportional hazard is rejected. The maximum time over which the restricted mean was to be calculated in 4 years.

Results

[0314] The 63-gene signature is prognostic in high grade serous (HGS) ovarian patients in the control arm (receiving carboplatin plus paclitaxel chemotherapy treatment) of ICON7 trial data. The results using Cox proportional hazards regression show that patients classified to the 'immune' molecular subgroup by the gene signature have a statistically significant improved progression free survival compared to those classified as pro-angiogenic before (Univariate HR=0.48, 95% CI=0.32, 0.72; $p<0.001$) and after (Multivariable HR=0.50; 95% CI=0.32, 0.79; $p=0.003$) adjusting for other clinical covariates including age, grade, ECOG, debulking status and stage see FIG. 7A Similarly, patients classified into immune molecular subgroup had a statistically significant better overall survival compared to the pro-angiogenic before (Univariate HR=0.46; 95% CI=0.26, 0.80; $p=0.006$) and after (Multivariable HR=0.53; 95% CI=0.29, 0.97; $p=0.041$) adjusting for other clinical covariates see FIG. 7B. The data show no serious departure of the proportionality assumption.

Example 4

Predictive Utility of Non-Angiogenesis Signature in Colorectal Cancer

[0315] A public array data set obtained from the Gene Expression Omnibus database for a cohort of recurrent or metastatic colorectal cancer responders and non-responders to Bevacizumab on plus 2 arrays (E-GEOD-19862) was obtained and analyzed using the example 63 gene signature

of Table 2. The 63 gene ovarian immune signatures predicts response to bevacizumab with an AUC: 0.86 (0.60-1.00). See FIG. 8.

Example 5

Summary of 63 Gene Signature

Samples:

- [0316]** Internal training samples: This sample set comprised of 193 High Grade Serous Ovarian samples retrieved from the Edinburgh Ovarian Cancer Database
- [0317]** Tothill samples: This is a publically available dataset, from which 152 High Grade Serous Ovarian samples were used for analysis
- [0318]** ICON7 samples: This sample set comprises of 284 High Grade Serous samples from a phase III randomized trial of carboplatin and paclitaxel with or without bevacizumab first line cancer treatment which were accessed through the MRC (Medical Research Council).
- [0319]** ICON7 SOC (Standard of Care)—140 samples—refers to patients who did not receive the addition of bevacizumab
- [0320]** ICON7 Immune group—116 samples: this refers to the ICON7 samples predicted in the Immune group by the Immune 63 gene signature
- [0321]** ICON7 ProAngio group—168 samples: this refers to the ICON7 samples predicted in the ProAngiogenesis group by the Immune 63 gene signature

Methods:

Signature Development

[0322] A balanced sample set of 193 Ovarian HGS samples were used to develop the signature using the PLS (Dejong S. Simpls—an Alternative Approach to Partial Least-Squares Regression. Chemometr Intell Lab 1993; 18:251-63) (Partial Least Squares) method during 10 repeats of 5-fold cross validation (CV). The following steps were used within signature development:

- [0323]** Probesets mapped to genes and gene expression measured using the $\log_2$ transformation of the median probeset expression for each gene
- [0324]** Within nested CV, quantile normalization was performed following a pre-filtering to remove 75% of genes with low variance, low intensity, and high correlation to cDNA yield
- [0325]** Genes/features were ranking based on correlation adjusted t-scores and feature reduction involved discarding 10% of the least important genes until 5 genes remained
- [0326]** The 63 gene signature was identified as the feature set for which the hazard ratio (HR) predicting Progression free survival (PFS) under cross-validation was optimal

The following datasets have been evaluated within CV to determine the performance of the 63 gene signature:

- [0327]** Internal training set—193 samples
- [0328]** ICON7 SOC (Standard of Care)—140 samples
- [0329]** ICON7 Immune group—116 samples
- [0330]** ICON7 ProAngio group—168 samples

Core Gene Analysis

[0331] The purpose of evaluating the core gene set of the signature is to determine a ranking for the genes based upon their impact on performance when removed from the signature.

This analysis involved 1,000,000 random samplings of 10 signature genes from the original 63 signature gene set. At each iteration, 10 randomly selected signature genes were removed and the performance of the remaining 53 genes was evaluated using the PFS endpoint to determine the impact on HR performance when these 10 genes were removed in the following 3 datasets:

[0332] Internal Validation—72 samples

[0333] Tothill HGS (Tothill R W, Tinker A V, George J, et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin Cancer Res 2008; 14:5198-208) (High Grade Serous)—152 samples

[0334] ICON7 SOC (Standard of Care)—140 samples

Within each of these 3 datasets, the signature genes were weighted based upon the change in HR performance (Delta HR) based upon their inclusion or exclusion. Genes ranked '1' have the most negative impact on performance when removed and those ranked '63' have the least impact on performance when removed.

Minimum Gene Analysis

[0335] The purpose of evaluating the minimum number of genes is to determine if significant performance can be achieved within smaller subsets of the original signature.

This analysis involved 10,000 random samplings of the 63 signature genes starting at 1 gene/feature, up to a maximum of 25 genes/features. For each randomly selected feature length, the signature was redeveloped using the PLS machine learning method under CV and model parameters derived. At each feature length, all randomly selected signatures were applied to calculate signature scores for the following 3 datasets:

[0336] Tothill HGS (High Grade Serous)—152 samples

[0337] ICON7 SOC (Standard of Care)—140 samples

[0338] ICON7 Immune group—116 samples

Continuous signature scores were evaluated with PFS (Progression Free Survival) to determine the HR (Hazard Ratio) effect. The HR for all random signatures at each feature length was summarized and figures generated to visualize the performance over CV.

Results

Signature Development

[0339] This section presents the results of signature development within CV.

[0340] Internal training set: FIGS. 9, 10 & 11 show the AUC (Area under the receiver operating curve), C-Index (Concordance Index) & HR of the training set, from which the 63 gene signature was identified.

[0341] ICON7 SOC: FIGS. 12 & 13 show the HR and C-Index of the ICON7 SOC samples under CV.

[0342] ICON7 Immune group: FIG. 14 shows the HR of the ICON7 Immune samples (as identified by the 63 gene signature) under CV.

[0343] ICON7 ProAngio group: FIG. 15 shows the HR of the ICON7 ProAngio samples (as identified by the 63 gene signature) under CV.

Core Gene Analysis

[0344] The results for the core gene analysis of the 63 gene signature in 3 datasets is provided in this section.

[0345] Internal Validation: Delta HR performance measured in this dataset for the 63 signature genes is shown in FIG. 16. This figure highlights the top 10 ranked genes in the signature which are the most important in retaining a good HR performance within this dataset.

[0346] Tothill HGS: Delta HR performance measured in this dataset for the 63 signature genes is shown in FIG. 17. This figure highlights the top 10 ranked genes in the signature which are the most important in retaining a good HR performance within this dataset.

[0347] ICON7 SOC: Delta HR performance measured in this dataset for the 63 signature genes is shown in FIG. 18. This figure highlights the top 10 ranked genes in the signature which are the most important in retaining a good HR performance within this dataset.

[0348] Delta HR across these 3 datasets was evaluated to obtain a combined gene ranking for each of the signature genes. The ranks assigned to the signature genes based on the core set analysis have been outlined in Immune63GeneSig_CoreGenes_HR.txt.

Minimum Gene Analysis

[0349] The results for the minimum gene analysis of the 63 gene signature in 3 datasets is provided in this section.

[0350] Tothill HGS: The average HR performance measured in this dataset using the random sampling of the signature genes from a feature length of 1.25 is shown in FIG. 19. This figure shows that to retain a significant HR performance (i.e. HR<1) a minimum of 5 of the signature genes must be selected.

[0351] ICON7 SOC: The average HR performance measured in this dataset using the random sampling of the signature genes from a feature length of 1.25 is shown in FIG. 20. This figure shows that to retain a significant HR performance (i.e. HR<1) a minimum of 2 of the signature genes must be selected.

[0352] ICON7 Immune: The average HR performance measured in this dataset using the random sampling of the signature genes from a feature length of 1.25 is shown in FIG. 21. This figure shows that to retain a significant HR performance (i.e. HR<1) a minimum of 5 of the signature genes must be selected.

In summary, it is recommended that a minimum of at least 5 genes can be used and significant performance will be retained.

Example 6

Colon Cancer Samples

Samples and Methods

Samples

[0353] 529 fresh-frozen (FF) primary tumour samples from patients with stage II, III or IV disease, 232 of which had progression free survival data followed up after receiv-

ing adjuvant chemotherapy, were assessed with the 63-gene signature. Microarray data from gene expression profiling on the Affymetrix U133 Plus 2.0 platform was obtained from the public domain (GEO accession number GSE40967).

Signature Score Calculation

[0354] Signature scores were calculated using the following steps:

- [0355] Robust Multi-array Analysis (RMA) background correction.
- [0356] Summarisation of probes to probesets using median expression.
- [0357] Summarisation of probesets to genes using median expression
- [0358] A quantile normalisation model is applied to the gene level matrix (or vector) on a per sample basis, which transforms the distribution of individual patient gene profiles to a similar distribution as the training data.
- [0359] The signature score is calculated per sample using a weighted sum of the expression of each gene in the signature:

$$\text{Signature Score} = \sum_i w_i \times (x_i - b_i) + k$$

- [0360] Where w_i is a weight for each gene, b_i is a gene-specific bias, x_i is the observed gene expression level after pre-processing and $k=0.2953$ is a constant offset

Statistical Analysis

[0361] Cox's proportional hazard regression model is used to estimate the univariate hazard ratio (HR) effect of the 63-gene signature on progression free survival following adjuvant chemotherapy. The p-value for the HR estimate is calculated using the log-rank test.

Results

[0362] FIG. 22 provides the Kaplan Meier curve for the signature predictions in 232 patients that received adjuvant chemotherapy, showing that the 63 gene signature can be used to predict prognosis. The univariate HR calculated from Cox's proportional hazard regression is 0.49 with log-rank $p=0.001$. "Angio on" is equivalent to negative for the biomarker signature and "Angio off" is equivalent to positive for the biomarker signature.

Example 7

Prognostic Utility of Subtype in Colorectal Cancer

Samples

[0363] A public array data set was obtained from the Gene Expression Omnibus database (GSE40967) comprising a cohort of 529 patients with colorectal cancer (Marrisa et al, 2013). Samples were profiled on the Affymetrix Plus 2.0 array platform. The data comprises patients with stage II, III and IV disease, and 232 patients received adjuvant chemotherapy with follow up recurrence free survival (RFS) data.

Methods

[0364] All samples were pre-processed using RMA and semi-supervised hierarchical clustering was performed using the Entrez Gene IDs defining the "angiogenesis" gene cluster (cluster 4) in FIG. 1 to filter the data matrix. Following standardization of the filtered data matrix to the median gene expression values, agglomerative hierarchical clustering was performed using Euclidean distance and Ward's linkage method. The optimal number of sample and gene clusters was determined using the GAP statistic. As the gene list used to cluster the samples was highly enriched for the angiogenesis biology, samples clusters with up-regulation of these genes were class labelled angiogenesis active (or angio on); and those with down-regulation of these genes were class labelled angiogenesis inactive (or angio off).

The samples were further tested with the 63-gene signature and an association between the 63 gene signature score and the sample clusters (angiogenesis active or angiogenesis inactive) was evaluated using the Area Under the Receiver Operating Characteristic (ROC) Curve (AUC). The threshold for classifying patients as angiogenesis active/inactive within colorectal cancer was optimised to maximise the sensitivity+specificity with respect to predicting the subtype as defined by the hierarchical clustering analysis.

The clinical significance of the 63-gene signature predictions was evaluated using Kaplan Meier curves and Cox-proportional hazard survival analysis. The endpoint was defined as a progression free survival, and the Cox-proportional hazards modelling included an adjustment for clinical covariates: age; gender; stage; tumour location and MSI status.

Results

[0365] 520 samples underwent semi-supervised clustering based on 219 genes (the genes defining cluster 4 in FIG. 23). Two sample clusters and 3 gene clusters were identified (FIG. 23). Sample cluster 1 (273 patients) was characterised by up-regulation of expression of angiogenesis genes, therefore was labelled angiogenesis active; and sample cluster 2 (256 patients) was characterised by down-regulation of expression of angiogenesis genes, therefore was labelled angiogenesis inactive.

The AUC calculated for the 63-gene signature with respect to predicting the two sample clusters was 0.86 [0.83-0.89], as depicted in the ROC curve in FIG. 24. The maximum sum of sensitivity and specificity for predicting the subtype was defined at a signature score threshold of 0.6604; and this is the threshold that is applied to predict patients as being in the angiogenesis active or angiogenesis inactive subtype. Patients with a signature score >0.6604 are classified as angiogenesis active and patients with a signature score ≤ 0.6604 are classified as angiogenesis inactive.

Cox-proportional hazard modelling of progression free survival predicted by the signature (adjusting for clinical covariates) revealed that patients in the angiogenesis inactive group had significantly improved progression free survival compared to patients in the angiogenesis active group (Table 4: HR=0.47 [0.30-0.76]). Kaplan Meier curve is shown in FIG. 22.

TABLE 4

Multivariable survival analysis results using the 232 adjuvant treated patients	
Predictive variable	HR [95% CI]
Assay Positive	0.47 [0.30-0.76]
Stage (II)	1.37 [0.74-2.55]
III	3.24 [1.45-7.23]
IV	
Tumour location	1.68 [0.99-2.85]
Age	1.01 [0.99-1.03]
Sex	1.23 [0.79-1.92]
MMR	0.91 [0.32-2.62]

Example 8

Independent Validation of Prognostic Utility of 63-Gene Signature

Samples

[0366] A public array data set was obtained from the Gene Expression Omnibus database (GSE14333) comprising a cohort of 290 patients with colorectal cancer (Jorissen et al, 2009). Samples were profiled on the Affymetrix Plus 2.0 platform. 87 patients received adjuvant chemotherapy with follow up recurrence free survival (RFS)

Methods

[0367] The samples were tested with the 63-gene signature classified as being angiogenesis active or angiogenesis inactive using the threshold of 0.6604 as defined in Example 5. The clinical significance of the 63-gene signature predictions was evaluated using Kaplan Meier curves and Cox-proportional hazard survival analysis. The endpoint was defined as a progression free survival, and the Cox-proportional hazards modelling included an adjustment for all available clinical covariates: age; gender; stage and tumour location.

Results

[0368] 159 patients received a signature score >0.6604 and were classified as angiogenesis active; and 131 patients received a signature score ≤0.6604 and were classified as angiogenesis inactive. Cox-proportional hazard modelling of progression free survival predicted by the signature (adjusting for clinical covariates) revealed that patients in the angiogenesis inactive group had significantly improved progression free survival compared to patients in the angiogenesis active group (Table 5: HR=0.33 [0.14-0.83]). Kaplan Meier curve is shown in FIG. 25.

TABLE 5

Multivariable survival analysis results using the 87 adjuvant treated patients	
Predictive variable	HR [95% CI]
Assay Positive	0.33 [0.14-0.83]
Stage (III)	1.03 [0.41-2.59]
Tumour location (Left)	Rec 0.40 [0.08-1.95]
	Right 0.50 [0.20-1.23]

TABLE 5-continued

Multivariable survival analysis results using the 87 adjuvant treated patients	
Predictive variable	HR [95% CI]
Age	1.01 [0.98-1.04]
Sex	1.13 [0.47-2.68]

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accgtggttc ctgagctaac tgcattccct acccaggcag agactgtcct atgctctgag	180
cttccaaaag agactcagac cgcgacacag ccaccgtatt tatggaatga c	231

<210> SEQ ID NO 8
 <211> LENGTH: 245
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

gaaatacgaa tgtagagatc cctaatacatc aaattgttga ttgaaagact gatcataaac	60
caatgctggt attgcacett ctggaactat gggcttgaga aaacccccag gatcacttct	120
ccttggtctc cttcttttct gtgcttgcat cagtgtggac tcctagaacg tgcgacctgc	180
ctcaagaaaa tgcagttttc aaaaacagac tcagattcca gcctccaatg aataagacat	240
cttcc	245

<210> SEQ ID NO 9
 <211> LENGTH: 115
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 9

tgaacaaatg gcctttatta aaaactgagt gactctatat agctgatcag ttttttcacc 60
tggaagcatt tgtttttact ttgatatgac tgtttttcgg acagtttatt tgttg 115

<210> SEQ ID NO 10

<211> LENGTH: 179

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

tgtggtagcc tcacttttaa tgaacaaatg gcctttatta aaaactgagt gactctatat 60
agctgatcag ttttttcacc tggaagcatt tgtttttact ttgatatgac tgtttttcgg 120
acagtttatt tgttgagagt gtgacaaaaa gttacatggt tgcacctttt tagttgaaa 179

<210> SEQ ID NO 11

<211> LENGTH: 113

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

caaagtgcata ataattaact caaccaggtc tactttttaa tggctttcat aacactaact 60
cataaggtta ccgatcaatg catttcatac ggatatagac ctagggtctt gga 113

<210> SEQ ID NO 12

<211> LENGTH: 92

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

gctgagcaaa gcagactacg agaaacacaa agtttacgcc tgcaagtcac cccatcaggg 60
cctgagctcg cccgtcaca agagcttcaa ca 92

<210> SEQ ID NO 13

<211> LENGTH: 298

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

agcagactac gagaacacaca aagtttacgc ctgcaagtc acccatcagg gcctgagctc 60
gcccgtcaca aagagcttca acaggggaga gtgttagagg gagaagtgcc cccacctgct 120
cctcagttcc agcctgaccc cctcccatcc ttggcctct gacccttttt ccacagggga 180
cctaccccta ttgcggctct ccagctcacc ttccacctca cccccctcct cctccttggc 240
tttaattatg ctaatgttgg aggagaatga ataaataaag tgaatctttg cacctgtg 298

<210> SEQ ID NO 14

<211> LENGTH: 86

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

actgaggggg tcctggtgtg catttgcacc ctaaagctgc ttacggtgaa aaggcaaata 60
ggtatagcta ttttgcaggc accttt 86

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<210> SEQ ID NO 15
 <211> LENGTH: 158
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 15

 tttggtgcag tttccagggt gcagtacagc agggcctgaa tactggccct ggactccctt 60
 ttccagaaca ccagggtgtg ccacctgggg ctcagggtaca cagtgggggc tctcggaagc 120
 caccgtgtgg ttctttcaca ggcacgttta ttttgctg 158

 <210> SEQ ID NO 16
 <211> LENGTH: 223
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 16

 tggatcatgag aagaaggtaa tttccagcct tcaagaagac agacatttag aagaagagct 60
 gaaatgtcag gaacaaaaag aagaacagct gcaggaagggt gtgcaccgga aggagcccca 120
 gggggccacg tagcagcggc tcagtgggtg gccatcgatt tggaccgtcc cctgcccact 180
 tgctccccgt gagcactgcg tacaacatc caaaagttca aca 223

 <210> SEQ ID NO 17
 <211> LENGTH: 262
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 17

 ccaggttagg aaaggattca gcactacagc ataccctctt acaacatata gccctgtcac 60
 attgagatca taatccctcc tgtccactc ctctctacca accccacct actagctagg 120
 tcttcagtgt tttacattga atattggtac attttaatta ttttttctca taaatgggtt 180
 atttatagaa attttgttaa ctcttgagcc atatgcatgt gtagatactg gcagggtat 240
 gtttgtttat gatgctctgc aa 262

 <210> SEQ ID NO 18
 <211> LENGTH: 245
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 18

 attgtgctat aatccctatt tagttcaaaa ttaaccagaa tttttccatg tgaatggac 60
 caaactcata ttattgttat gtaatacag agttttaatg cagtatgaca tcccacaggg 120
 gaaaagaatg tctgtagtgg gtgactgtta tcaaatattt tatagaatac aatgaacggt 180
 gaacagactg gtaacttgtt tgagttccca tgacagattt gagacttgtc aatagcaaat 240
 cattt 245

 <210> SEQ ID NO 19
 <211> LENGTH: 202
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 19

 taatgggttaa cgaaccgggt cgacatcaca aaggagggtg gagactcttt ttactaactt 60
 gaatgagaca aaagcagtgg tgcagttta taatcctgat gcatttcagt aataatgtag 120

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aaaaacatta ttttaaaaaa gttccaacac acagccatga ggagcctcag ttttgaaaga 180

ggtgcataat aaaactacta ac 202

<210> SEQ ID NO 20

<211> LENGTH: 132

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

acagcccacc cttgtgtoca ctgtgacccc tgttcccatg ctgacctgtg tttctccccc 60

agtcattcttt cttgttccag agagggtggg ctggatgtct ccattctctgt ctcaacttta 120

tgtgcactga gc 132

<210> SEQ ID NO 21

<211> LENGTH: 53

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

aagcaagata tcaatgtagc agaattgcac ttgtgcctca cgaacatata taa 53

<210> SEQ ID NO 22

<211> LENGTH: 151

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

ttggaatggt gtagttaoct actgagtagg cggcgatttt tgtatgttat gaacatgcag 60

ttcattatgt tgtggttcta ttttactttg tacttgtgtt tgcttaaaca aagtgactgt 120

ttggcttata aacacattga atgcgcttta t 151

<210> SEQ ID NO 23

<211> LENGTH: 205

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

aatcccaatt ttcaggagtg gtggtgtcaa taaacgctct gtggccagtg taaaagaaaa 60

tccctcgcag ttgtggacat tctgttccct gtccagatac catttttccct agtatttctt 120

tgttatgtcc cagaactgat gttttttttt taagggtactg aaaagaaatg aagttgatgt 180

atgtcccaag ttttgatgaa actgt 205

<210> SEQ ID NO 24

<211> LENGTH: 269

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

gcctggcctg attcagggcc ttgtggcccc cagcttctgt ttcaagctgg gcagacccca 60

ggatcccttc cctccctaag gactcagctg aggggcccct ctgccccctt ctacctccac 120

ctcagcacc cccccagct tgatgtttgg gtctccccag caccctcctc cctggccggt 180

gcaaagtaca gggaggtaaa gcaggaccct tgcagacatg ttgccagca cacagtaggc 240

cctcaataaa agccatttgc acttttaaat 269

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<210> SEQ ID NO 25

<211> LENGTH: 169

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

gagaagtcac tcacactggc cacaaggacg ctggctactg tctattaaaa tttgatgtt 60

tctgtgaaat tctcagagtg ttttaattgta ctcaatggta tcattacaat tttctgtaag 120

agaaaatatt acttatttat cctagtattc ctaacctgtc agaataata 169

<210> SEQ ID NO 26

<211> LENGTH: 234

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

ctgtggcatg ctcagagggt cctgctggat tccagctgga gcggtgtgat acccttcttt 60

ttcagctgtt cgtgccttcc tttcttgtat ccaccaaagt ggagacaaat acatgatctt 120

aaagatacac agtacctact taattccagc tgatgggaga ccaaagaatt tgcaagtgga 180

tggtttggtg tcaactgtaaa taaaaagagg gcctgggaat tcttgcgatt ccat 234

<210> SEQ ID NO 27

<211> LENGTH: 232

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

tgaacaaaa tagagtcagc tgaccagca tcagccacac tttgggttgg aaaatgtttg 60

cctgttgtaa ttaatttaag cttaagtata tatcaacatt attttattgt gcaattaaaa 120

caatacaaat tcattggtttt ttaaagttaa aaattttaac cactgtaaca acagtttttg 180

tgttattttc tgtattaaac atcttggtgc acgcatttga ggtcatcagg gt 232

<210> SEQ ID NO 28

<211> LENGTH: 147

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

atgttcatag gttctcaacc ctcaccccc accacgggag actagagctg caggatccca 60

ggggaggggt ctctcctccc accccaaggc atcaagccct tctccctgca ctcaataaac 120

cctcaatata tattctcatt gtcaatc 147

<210> SEQ ID NO 29

<211> LENGTH: 149

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

aatgttcata ggttctaaac cctcaccccc cccacgggag actagagctg caggatccca 60

ggggaggggt ctctcctccc accccaaggc atcaagccct tctccctgca ctcaataaac 120

cctcaataaa tattctcatt gtcaatcag 149

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<210> SEQ ID NO 30
<211> LENGTH: 152
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

aatgttcata ggttctaaac cctcaccccc cccacgggag actagagctg caggatccca	60
ggggagggggt ctctcctccc accccaaggc atcaagccct tctccctgca ctcaataaac	120
cctcaataaa tattctcatt gtcaatcagc aa	152

<210> SEQ ID NO 31
<211> LENGTH: 150
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

aatgttcata ggttctcaac cctcaccccc caccacggga gactagagct gcaggatccc	60
aggggagggg tctctctccc caccacaagg catcaagccc ttctccctgc actcaataaa	120
ccctcaataa atattctcat tgcaatcag	150

<210> SEQ ID NO 32
<211> LENGTH: 151
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

atgttcatag gttctcaacc ctcacccccc ccacgggaga ctagagctgc aggatcccag	60
gggagggggtc tctcctccca ccccaaggca tcaagccctt ctccctgcac tcaataaacc	120
ctcaataaat attctcattg tcaatcagca a	151

<210> SEQ ID NO 33
<211> LENGTH: 254
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

gcagctatatt gagcctgacg cctgagcagt ggaagtccca cagaagctac agctgccagg	60
tcacgcatga agggagcacc gtggagaaga cagtggcccc tacagaatgt tcataggttc	120
taaaccctca cccccccac gggagactag agctgcagga tcccaggga ggggtctctc	180
ctcccacccc aaggcatcaa gcccttctcc ctgcactcaa taaaccctca ataaatattc	240
tcattgtcaa tcag	254

<210> SEQ ID NO 34
<211> LENGTH: 239
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

aagaacaact cctcaccagt tcattcctgag gctgggagga ccgggatgct ggattctgtt	60
ttccgaagtc actgcagcgg atgatggaac tgaatcgata cgggtgtttc tgtccctcct	120
actttccttc acaccagaca gccctcctg tctccaggac aggacaggac tacagacaac	180
tctttcttta aataaattaa gtctttacaa taaaaacaca actgc aaagt accttcata	239

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<210> SEQ ID NO 35
<211> LENGTH: 270
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

gaaagagcat cgttccaatg cttgttcact gttcctctgt catactgtat ctggaatgct      60
ttgtaataact tgcattgctt ttagaccaga acatgtaggt ccccttggtg ctcaatactt      120
tttttttctt aattgcattt gttggctcta ttttaatttt tttcttttaa aataaacagc      180
tgggaccatc ccaaaagaca agccatgcat acaactttgg tcatgtatct ctgcaaagca      240
tcaaattaaa tgcacgcttt tgcattgtca                                     270

<210> SEQ ID NO 36
<211> LENGTH: 97
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

ttctcccaaa ccacttagta gcaacgctac cccagggggt aatgactgca cactgggctt      60
cttttcagaa tgaccctaac gagacacatt tgcccaa                                97

<210> SEQ ID NO 37
<211> LENGTH: 213
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

tgtgttgggg tagactgtc ctgcagagtt tggaagaagt caccagcaaa gccggcctaa      60
ccaagaaaag tcaaggccct tcatgacctt gctgggcaca gaaaacaccc tcgtggagta      120
cactaatttg aactggactg gtctcagtgt gagcacttgg cacactttac taaacacata      180
tacaacccca cgtgagtc actttaaagt aaa                                     213

<210> SEQ ID NO 38
<211> LENGTH: 151
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

tgtaatgcta aaactgaaat ggtccgtgtt tgcattgtta aaaatgatgt gtgaaataga      60
atgagtgtcta tgggtgtgaa aactgcagtg tccgttatga gtgccaaaaa tttgtcttga      120
aggcagctac actttgaagt ggtctttgaa t                                     151

<210> SEQ ID NO 39
<211> LENGTH: 116
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

ctgggccttg gtccccagaa gatggcggct agggcctcgc cgccaggaca gagaagggac      60
ggggtggctg ggcagtcagg gaaggagggt cgccgggac cgacattttg gagaga          116

<210> SEQ ID NO 40
<211> LENGTH: 220
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 40

```
gaacaggaac gccttctcaa ggagggatc gagaatgaga gcaagagact tcaaaaagac    60
atatgggata tccagatgag aagcaaatca ttggagccaa tatgtaacat actttaaaag    120
tccaaggagc aaaatttgcc tgtccagctc cctctcccca agaaacaaca tgaatgagca    180
acttcagagt gtcaaacaac tgccattaaa cttaactcaa                            220
```

<210> SEQ ID NO 41

<211> LENGTH: 232

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

```
tttgttagta catttcagtg tagtcattca tttctagctg tacataggat gaaggagaga    60
tcagatacat gaacatgttt tacatggggt gctgtattta gaattataaa catttttcat    120
tattggaaag tgtaacgggg accttttgca tacctgttta gaacaaaaac caccatgaca    180
cagtttttat agtgtctgta tattttgtgat gcaatgggtc tgtaaagggt tt          232
```

<210> SEQ ID NO 42

<211> LENGTH: 53

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

```
gaccaggaat tcggcttcga cgttgccct gtctgcttcc tgtaaaactcc ctc          53
```

<210> SEQ ID NO 43

<211> LENGTH: 132

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

```
aaaagtccac agtcaaatgg ggaggggtat ttttcatgca ggagacccca ggccctggag    60
gctgcaacat acctcaatcc tgtcccaggc cggatcctcc tgaagccctt ttcgcagcac    120
tgctatcctc ca                                                            132
```

<210> SEQ ID NO 44

<211> LENGTH: 287

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

```
agtgagactg actgcaagcc ccaccctcct tgagactgga gctggcgtct gcatacgaga    60
gacttggttg aacttggttg gtccttgtct gcaccctcga caagaccaca ctttgggact    120
tgaggagctgg ggctgaagtt gctctgtacc catgaactcc cagtttgcca attatagaga    180
caatctatct tgttacttgc acttggtatt cgaaccactg agagcgagat gggaagcata    240
gatatctata tttttatctt tactatgagg gccttgtaat aaatttc                    287
```

<210> SEQ ID NO 45

<211> LENGTH: 157

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

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tatgaattcc attcaaatcg ttcctttttg ttaacaaggg gcatggggag ggggtgggggt	60
gggggggag aggcgtctga cccaggaac ctgcaggcg gggctgggtc ggtgcccttt	120
aaggacaatt ttgacctgt tcaaccttc cacaaag	157

<210> SEQ ID NO 46
 <211> LENGTH: 212
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

gatgcatgag gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa	60
atgagtgcga cggccggcaa gccccgcgc cccaggctct cggggctcgc cgaggatgct	120
tggcacgtac cccgtgtaca tacttcccg gcgccagca tggaaataaa gcaccagcg	180
ctgccctggg cccctgcga actttcttgt ac	212

<210> SEQ ID NO 47
 <211> LENGTH: 262
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

gtcctctcta tcttgatga gctcatgaac atttctcttg tgttctgac tcttcccaa	60
tgaacacctt tctgccacc caagctttgc tctcctctc tgtgagctct gggttccca	120
gtttgtttac ccgggaaagt acgtctagat tgtgtggtt gcctcattgt gctatttgcc	180
cactttcctt cctgaagaa atatctgtga accttcttc tgttcagtc taaaattcga	240
aataaagtga gactatgggt ca	262

<210> SEQ ID NO 48
 <211> LENGTH: 135
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

gggccagct cagaacggg cagacacccc cttcaaatgt ctcgcacgt aggttttgca	60
cagtgtttat ttgctggtgt ctcagggtt tgacagtttc cttaatatcc ccacacatgg	120
ccgagaaaaa taaat	135

<210> SEQ ID NO 49
 <211> LENGTH: 235
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

ttctacacta gtgccatggg aaccaggctt gaaaaagtag agagaagtga aagtagagtc	60
tgggaagttag ctgcctataa ctgagactag acggaaaagg aatactcgtg tattttaaga	120
tatgaatgtg actcaagact cgaggccgat acgaggctgt gattctgcct ttggatggat	180
gttgcgtgac acagatgcta cagacttgta ctaacacacc gtaatttggc atttg	235

<210> SEQ ID NO 50
 <211> LENGTH: 236
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 50

attggagtg atgggttctg ccttaaattg ggaggactcc aagccgggaa ggaaaattcc	60
cttttccaac ctgtatcaat ttttacaact tttttcctga aagcagttta gtccatactt	120
tgcaactgaca tactttttcc ttctgtgcta aggtaaggta tccaccctcg atgcaatcca	180
ccttgtgttt tcttaggggtg gaatgtgatg ttcagcagca aacttgcaac agactg	236

<210> SEQ ID NO 51

<211> LENGTH: 243

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

gggatctcct tttgtgaaaa ccagtttgat gtgctaaaag taaaaagtct attttccagt	60
gtggtcttgt tcagaagcag ccagatttcc aatgttggtt tccccctcca ctcagaaacc	120
cctgcccttt cccttcagaa aacgatggca ggcattcctt tgagtttaca agcagagact	180
cactccaacc caaactagct gggagttcag aacctgggtg gaataaagaa atgtgcatct	240
ggt	243

<210> SEQ ID NO 52

<211> LENGTH: 221

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

cctgtaagac aataggccat gttaattaaa ctgaagaagg atatatttgg ctgggtgttt	60
tcaaatgtca gcttaaaatt ggtaattgaa tggaagcaaa attataagaa gaggaaatta	120
aagtcctcca ttgcatgtat tgtaaacaga aggagatggg tgattccttc aattcaaaag	180
ctctctttgg aatgaacaat gtgggctgtt gtaaattctg g	221

<210> SEQ ID NO 53

<211> LENGTH: 225

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

gagtaccgcg cagacattaa aagtcattga aaagaacatt tgactgaaag aaaaatgctc	60
cttgaatatt aaaaggttgt aaaaatagtg catgttatgt gatttcaatt ttgtttttta	120
aaatatgggt gtatgcttgt atacgtagag cagataaaaa agacggaagg cataactaaa	180
aatgttgagt gggtatcttt gtatggtgga acaaagtcac tgtaa	225

<210> SEQ ID NO 54

<211> LENGTH: 182

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

atgctgagtg acactcttgt gtatatttcc aaatttttgt acagtcgctg cacatatttg	60
aaatcatata ttaagacttt ccaagatga ggtccctggg ttttcatggc aacttgatca	120
gtaaggattt cacctctgtt tgtaactaaa accatttact atatgttaga catgacattc	180
tt	182

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<210> SEQ ID NO 55
<211> LENGTH: 157
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55
tgtgttttca gagctaggta cagaggaatg ttgctacct ttagcgggtga aaaaagaaag 60
agagtcaaga attttgttgg attgtgtttg tgtgtgcata tatttgatat catcattata 120
tttghtaatct ttggacttgt aatcatagcc tgtttat 157

<210> SEQ ID NO 56
<211> LENGTH: 249
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56
tctccagagg gcacttcggc tgcctttgct tcctttcatt cgaggcccggt ctcttgctga 60
cagaatagggt tccgttttgg gcggtgggttc tcgagcctgc cattcaaaac caaagcaaatt 120
tggagcattt ctcacaacat ggtattgaag ttcctttttg ttctcaaaag ttgtgaccgt 180
gttaaattgt actcccttag tcctgtaagg tatgttaagt gaatcgcagt tacgctgtac 240
ttttattaa 249

<210> SEQ ID NO 57
<211> LENGTH: 73
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57
tctgtaattc attgagcagt tagctcattt gagataaagt caaatgccaac acactagctc 60
tgtattaatc ccc 73

<210> SEQ ID NO 58
<211> LENGTH: 123
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58
atgggtataat ggttgactgg gtttctctgt atagtactgg catgggtacgg agatgtttca 60
cgaagtttgt tcatcagact cctgtgcaac tttcccaatg tggcctaaaa atgcaacttc 120
ttt 123

<210> SEQ ID NO 59
<211> LENGTH: 292
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59
acagtgttgt atgaggtttg aggattttga tccaagctgg tccactcag tccatagcag 60
agaatgaaag ggcccagaga ggggtgtgac ctctgcctga agtcacacag tgagtcgagg 120
acaggagggt gaccccagggt ttctatgtgt agggcgggag gatgttttgg gacacagttc 180
aattctcatt tgtcacacac ttgtgctatt agagatcaac cccttcgctc ctgtgtcttg 240
caatggcagc cttggcaaac gctaaatgaa aatcgtgaca acacttgtgt ta 292

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<210> SEQ ID NO 60

<211> LENGTH: 223

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

```
tcatgttaaa gagccgtgtc tcccgccagc actcctcacc ccggtatgaa tgtgtttcct    60
ccacattgta tatecttcca cctctgggt gcttagatca gtaataaaaa ttgatgtaat    120
ataatttata agtaacactg ttgaaacct gatccagtg gaggtgtaa cccacctgcc    180
cccgaccac cccctgacc cctgtaccg catttgtgtg tat                        223
```

<210> SEQ ID NO 61

<211> LENGTH: 275

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

```
gttatggtgc taatgtactt tcacttttaa actctagatc agaattgttg acttgcatc    60
agaacataaa tgcacaaaat ctgtacatgt ctcccatcag aaagattcat tggcatgcca    120
caggggattt tcctccttca tcctgtaaag gtcaacaata aaaaccaaat tatggggctg    180
cttttgtcac actagcatag agaattgtgt gaaatttaac tttgtaagct tgtatgtggt    240
tgttgatctt ttttttcctt acagacaccc ataat                        275
```

<210> SEQ ID NO 62

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

```
tgaggatgtc accaattaac cagaaatcca gttattttcc gccctcaaaa tgacagccat    60
ggccggccgg gtgcttttgg gggctcgtcg gggggacagc tccactttga ctggcacagt    120
ctttgcatgg agacttgagg agggagggct tgaggttggt gaggttaggt gcgtgtttcc    180
tgtgcaagtc aggacatcag tttgattaaa ggtggtgcca atttatttac atttaaaact    240
gtcaggggat aaaatgacat ccattaatt atattgttaa tcaatcacgt gtatag      296
```

<210> SEQ ID NO 63

<211> LENGTH: 108

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

```
acatgcagta ctgtataccc cccatccctc cctcgggtcca ctgaacttca gageagttcc    60
cattcctgcc ccgcccatct ttttgtgtct cgctgtgata gatcaata                108
```

<210> SEQ ID NO 64

<211> LENGTH: 243

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

```
acaaaagagc cagagttctg gacccatgtt tggagcattt gtagccttat tttttgcgt    60
gtgaatcttt tacctgaaa aaaagcata atgaattaag ccagactgac cacttgcttg    120
```

-continued

gagtgtgtgc ttgaaaaaac cagagcaata ctgttgggta ttgtatcagg cttcagtaca	180
aactggtaac accaatgttg atcctgacag ctttcagttt tagcaaaaat acacgtgaaa	240
tct	243

<210> SEQ ID NO 65
 <211> LENGTH: 52
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

agtgcaacgt attcaagtcc tcaatatcct gatcataata ccatgctata gg	52
---	----

<210> SEQ ID NO 66
 <211> LENGTH: 286
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

actttgccgg cgagcacacc gcctaccgcg acggctgggt ggagacggcg gtcaagttgg	60
cgctgcgcgc cgccatcaag atcaacagcc ggaaggggcc tgcacggac acggccagcc	120
ccgaggggca cgcatttgac atggaggggc aggggcatgt gcatggggtg gccagcagcc	180
cctcgcatga cctggcaaag gaagaaggca gccaccctcc agtccaaggc cagttatctt	240
tccaaaacac gaccacacg aggacctcgc attaaagtat tttcgg	286

<210> SEQ ID NO 67
 <211> LENGTH: 168
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

catttcatgt ttggcgggca tgtgagtga caagatggaa agagcgattg gagcatcctg	60
gtataattac cccattgtg cttttaatgg aaatttcaaa ggacgggagt attttgttgg	120
ttggtgtcca gggttgggc actgttccaa gaggccttac acacacac	168

<210> SEQ ID NO 68
 <211> LENGTH: 150
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

aatgttcata ggtttctaac cctcaccccc caccacggga gactagagct gcaggatccc	60
aggggagggg tctctctccc caccacaagg catcaagccc ttctccctgc actcaataaa	120
ccctcaataa atattctcat tgtcaatcaa	150

<210> SEQ ID NO 69
 <211> LENGTH: 64
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

atgttcatag gttctcaacc ctcaccccc accacgggag actagagctc aggatcccag	60
ggga	64

-continued

<210> SEQ ID NO 70
<211> LENGTH: 167
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

tctgagcggg tcatggggca acacggtttag cggggagagc acggggtagc cggagaaggg	60
cctctggagc aggtctggag gggccatggg gcagtcctgg gtgtggggac acagtcgggt	120
tgaccaggg ctgtctccct ccagagcctc cctccggaca atgagtc	167

<210> SEQ ID NO 71
<211> LENGTH: 129
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

aatgcatatg gaggtaggct gaaaagaatg taatttttat tttctgaaat acagatttga	60
gctatcagac caacaaacct tccccctgaa aagtgcagcag caacgtaaaa acgtatgtga	120
agcctctct	129

<210> SEQ ID NO 72
<211> LENGTH: 150
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

aatgttcata gggtctcatc cctcaccccc caccacggga gactagagct gcaggatccc	60
aggggagggg tctctctctc caccacaagg catcaagccc ttctccctgc actcaataaa	120
ccctcaataa atattctcat tgccaatcaa	150

<210> SEQ ID NO 73
<211> LENGTH: 83
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

ttccaccatc aaatgctgta gaatgcttgg cactccctaa ccaaagtctg tctccataat	60
gccactgggtg ttaagatata ttt	83

<210> SEQ ID NO 74
<211> LENGTH: 121
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

atataccata ggctaaaaact aaggctttca ctctagaatg caaagctgtt ttgcagctgt	60
tttcccttaa agatgtcctg ttgctttagt gatatttaga cccctctcag ttaagaaatg	120
c	121

<210> SEQ ID NO 75
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

caagacctag gctcatggac gagatgggaa ggcacagga gaagggataa ccctacacc	60
---	----

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```

agaccccagg ctggacatgc tgactgtcct ctcccctcca gcctttggcc ttggcttttc 120
tagcctatatt acctgcaggc tgagccactc tcttcccttt cccagcctc actcccacag 180
gaagagccaa tgttttccac ccataatcct ttctgcccgc ccctagtccc ctctgctcag 240
ccaagcttgt tatcagcttt cagggccatg gttcacatta gaata 285

```

```

<210> SEQ ID NO 76
<211> LENGTH: 105
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 76

```

```

gtattttatt agtcacggat tattgtgcat caagcaattg ttaatatgac ctggctctat 60
ggggtagaac ttaggaaaaa taaagtttgt tcttattcaa ttttt 105

```

```

<210> SEQ ID NO 77
<211> LENGTH: 248
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 77

```

```

atgccctgag gccagttggc gaggggtggc tctgaggggt tttataccc ttgttttgc 60
aatgtttaat ttgcatcat aatttctaca ttgtccctga gtgtcagaac tataatttat 120
tccattttct tctgtgtctg tgccaagaaa cgcaggctct gggcctgccc ctgcccagg 180
aggccttgcc agcctgtgtg ctgtgtggaa cacctgttac ctgagcttac aggtaccaat 240
aaagaggc 248

```

```

<210> SEQ ID NO 78
<211> LENGTH: 55
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 78

```

```

atactggaac cctaactgca atgtggatgt ttaccacaca tgacttatta tgcat 55

```

```

<210> SEQ ID NO 79
<211> LENGTH: 237
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 79

```

```

agaagaccca cgtgctaggg gatgaggggc ttcctgggtc ctgttcccta cccatttgt 60
ggtcacagcc atgaagtcac cgggatgaac ctatccttcc agtggctcgc tccctgtagc 120
tctgcctccc tctccatata tcttccctcc acacctccct cccacacct cctactccc 180
ctgggcatct tctggcttga ctggatggaa ggagacttag gaacctacca gttggcc 237

```

```

<210> SEQ ID NO 80
<211> LENGTH: 151
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 80

```

```

gcagaaatat gtaaccttag actcagccag tttcctctgc agctgctaaa actacatgtg 60
gccagctcca ttctccaca ctgcgtacta catttctgc cttttcttt cagtgttttt 120

```

-continued

ctaagactaa ataaatagca aactttcacc t 151

<210> SEQ ID NO 81
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

taaagacgca tggttatgggtg ctaatgtact ttcactttta aactctagat cagaattggt 60
gacttgcatt cagaacataa atgcacaaaa tctgtacatg tctcccatca gaaagattca 120
ttggcatgcc acaggggatt ctctctcttc atcctgtaaa ggtcaacaat aaaaacccaaa 180
ttatggggct gcttttgtca cactagcata gagaatgtgt tgaaatttaa ctttgaagc 240
ttgtatgtgg ttgttgatct ttttttctct tacagacacc cataat 286

<210> SEQ ID NO 82
<211> LENGTH: 189
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

ttaccctcca aaagcaagta gccaaagccg ttgccaaacc ccaccataa atcaatgggc 60
cctttattta tgacgacttt atttattcta atatgatttt atagtattta tatatattgg 120
gtcgtctgct tcccttgat ttttcttct ttttttgtaa tattgaaaac gacgatataa 180
ttattataa 189

<210> SEQ ID NO 83
<211> LENGTH: 211
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

gtcaggtctt ggtaggtgcc tgcactgtgc tgccttctgg ctgacaatcc tggaaatctg 60
ttctccagaa tccaggccaa aaagttcaca gtcaaatggg gaggggtatt cttcatgcag 120
gagacccag gccctggagg ctgcaacata cctcaatcct gtcccaggcc ggatcctcct 180
gaagcccttt tcgcagcact gctatcctcc a 211

<210> SEQ ID NO 84
<211> LENGTH: 211
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

gaaaaaactt tctctttgcc atttcttctt cttctttttt aactgaaagc tgaatccttc 60
catttctctt gcacatctac ttgcttaaat tgtgggcaaa agagaaaaag aaggattgat 120
cagagcattg tgcaatacag ttccattaac tccttcccc gctcccccaa aaatttgaat 180
ttttttttca acactcttac acctgttatg g 211

<210> SEQ ID NO 85
<211> LENGTH: 89
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

-continued

tgactgaatt gctgaccott caagctctgt cttatccat tacctcaaag cagtcattcc 60

ttagtaaaagt ttccaacaaa tagaaatta 89

<210> SEQ ID NO 86

<211> LENGTH: 162

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

gcattctcaa gaggtcgtgc caatcagcca ctgaaaggaa aggcattcact atggactttc 60

tctatttttaa aatggtaaca atcagaggaa ctataagaac acctttagaa ataaaaatac 120

tgggatcaaa ctggcctgca aaacatagc cagttaattc tt 162

<210> SEQ ID NO 87

<211> LENGTH: 86

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

atcatttcat agtcatttat gtttcacgg tcctcatgtg tactagtgcg ttattttact 60

tatactcccg gatatcatat tatttta 86

<210> SEQ ID NO 88

<211> LENGTH: 146

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

atgttcatag gttctcaacc ctcaccccca ccacgggaga ctagagctgc aggatcccag 60

gggagggggtc tctcctccca cccaaggca tcaagccctt ctccctgcac tcaataaacc 120

ctcaataaat attctcattg tcaagg 146

<210> SEQ ID NO 89

<211> LENGTH: 186

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

gctgagcaaa gcagactacg agaaacacaa agtctacgcc tgcaagtca cccatcaggg 60

cctgagctcg ccggtcacia agagcttcaa caggggagag tggttagagg agaagtgcgc 120

ccacctgtc ctcagttcca gctgacccc ctcccatcct ttggcctctg accctttttc 180

cacagg 186

<210> SEQ ID NO 90

<211> LENGTH: 41

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

tacaagacca cgctcccggt gctggactcc gacggctcct t 41

<210> SEQ ID NO 91

<211> LENGTH: 211

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 91

```
gaaaaaactt tctctttgcc atttcttctt cttctttttt aactgaaagc tgaatccttc    60
catttcttct gcacatctac ttgcttaaat tgtgggcaaa agagaaaaag aaggattgat    120
cagagcattg tgcaatacag ttccattaac tccttccttc gctcccccaa aaatttgaat    180
ttttttttca acactcttac acctgttatg g                                211
```

<210> SEQ ID NO 92

<211> LENGTH: 105

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

```
ggacctgaag ggtgacatcc caggaggggc ctctgaaatt tcccacaccc cagcgccctgt    60
gctgaggact cctcccatgt ggccccaggt gccaccaata aaaat                    105
```

<210> SEQ ID NO 93

<211> LENGTH: 100

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

```
tgccccctt aagcgtagag gtgagcatgt ccttcacaat tgcacatgtc aagccatcag    60
caaggcgcat cacacaaaag gcaccaagac gtgaaacttt                        100
```

<210> SEQ ID NO 94

<211> LENGTH: 115

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

```
gcctgctcag tcttttcttc ttatctacaa tacaaaaggt ttgtctgaaa agtctggttt    60
tttttctttt tacaaatgta ccttagctgc atcaacagga gtaagatgta gaaaa        115
```

<210> SEQ ID NO 95

<211> LENGTH: 74

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

```
cgatatgact tccatgtaaa cgttcacca ctctgectgc ttacaccctg cctcatgct    60
aatgtaataa actc                                                    74
```

<210> SEQ ID NO 96

<211> LENGTH: 164

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

```
gtgtggatgc taagggtgtt gttttgtttt gtatttttat gtagcgcgtg ggtattgtgc    60
ctagaaatga agtcattatt agggatttaa atatgcaact catggagtgg atgagaccag    120
ctagaaagat aatagagtgt gaagaggaga tcggaaattc aata                    164
```

<210> SEQ ID NO 97

<211> LENGTH: 211

-continued

```

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97
gtttgtgtgg gaactttgca agtcagtttc cctgtatgaa gtgatggaga gagtgattaa    60
gatactgagc tttctctgtg ttcttgccgt taaccattgc cggtttgtgg gagattaaga    120
agtcgatgcg ttttatggag aattaattta ttttgatata gacagatgga cgggtcatga    180
aaatttgttg acatacttta ctaaactgct a                                  211

<210> SEQ ID NO 98
<211> LENGTH: 127
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98
tttttttagtt gccaacagtt gtatttttgc tgattattta tgaccttaaa taatatattt    60
ttttttttaa gaagacattt tgttacataa ggaaaacttt tttattcaat ggaataaatt    120
atggcat                                           127

<210> SEQ ID NO 99
<211> LENGTH: 251
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99
gaacaggagc aactactaaa agagggattt caaaaagaaa gcagaataat gaaaaatgag    60
atacaggatc tccagacgaa aatgagacga cgaaaggcat gtaccataag ctaaagacca    120
gagccttcct gtcaccctca accaaggcat aattgaaaca attttagaat ttggaacaag    180
cgtcactaca tttgataata attagatcct gcatacatac accaaaagtt tataaaggca    240
tgtggtacaa t                                           251

<210> SEQ ID NO 100
<211> LENGTH: 163
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100
ctttcattgg aagttcatca ctgttaggcg ttatcttgag tattataaca aagcaaatcc    60
acaagtattc aatataagat taggaaaaaa attcctgcga tactttgttg tcaaacactt    120
gccactgata gacgttatct tagcttttaa ggccctgtcac att                               163

<210> SEQ ID NO 101
<211> LENGTH: 258
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (61)..(61)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 101
atggagtata agctgtttgt agtcaggcct ggagtaatga gggtagctaa atactgaagg    60
natttttatg cagattgact gaaacctgaa tcaaattgga aggagagggc tgaattttga    120
tagactggaa gtattagaga attttctata ctttgactca aggaatgggc aacttttagg    180

```

-continued

aaaagcaact atattatgtc tgtaagatc atagaatctt aacctgaaag ggaccttgga 240

gactatttag tacaactc 258

<210> SEQ ID NO 102

<211> LENGTH: 193

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (120)..(125)

<223> OTHER INFORMATION: n is a, c, g, or t

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (127)..(127)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 102

gaagaaagct aactcagtag actaagagtg atttaccatgc ctgcaaataa tttgtgtctg 60

gggtcttgac cctcccaaaa tgcttctgta tttatatctc tgcttttaga taacagatgn 120

nnnnntntct atgggcttgt accggcagag gcaacagcag gtccttaaga ctccccaggt 180

gccatgatga aaa 193

<210> SEQ ID NO 103

<211> LENGTH: 173

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

gtaccatctt acatgcttaa ataactccac atttatttgt gtttattact ctgtgttata 60

aatatacatt tgttggcttc tctcttgat tattttgttt ctttgcctg taactaccac 120

tgaaagggtg caatacagct ttcttgaaat gtgtattgaa cggatgaatg tat 173

<210> SEQ ID NO 104

<211> LENGTH: 217

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

gttcccagtg acacttcaga gagctggtag ttagtagcat gttgagccag gcctgggtct 60

gtgtctcttt tctctttctc cttagtcttc tcatagcatt aactaatcta ttgggttcat 120

tattggaatt aacctggtgc tggatatttt caaattgtat ctagtgcagc tgattttaac 180

aataactact gtgttcctgg caatagtgtg ttctgat 217

<210> SEQ ID NO 105

<211> LENGTH: 233

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (35)..(35)

<223> OTHER INFORMATION: n is a, c, g, or t

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (53)..(53)

<223> OTHER INFORMATION: n is a, c, g, or t

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (60)..(60)

<223> OTHER INFORMATION: n is a, c, g, or t

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<400> SEQUENCE: 105

tggagtaaca cccagatctc tgcagcagtt aagcntgggg gcctagaact agnctagagn	60
tagaagaagg gacaaatgca atccgacctt tggatctaca cattcctctt gcttcaatgg	120
gtgtcattta agaattagag gaaaatatta ggagatggag aactagagtt gaggaaacca	180
aaagaagagg agtcacagaa aaccagctct ctctgtgcaa ggcattctga aag	233

<210> SEQ ID NO 106

<211> LENGTH: 178

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

ctttggatag aggtgaagaa ctgggacatg gctgtttcag gcagctgaag tcaaagggaa	60
tagtaattgg ggaaggggaa gtgggcagaa aggattgttg gccaatatac ctccactcc	120
agtagagagg gaggacttgg ctctgagaac ctccatctga cctaagagga accctcct	178

<210> SEQ ID NO 107

<211> LENGTH: 163

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

ctgcaaaagc cgagatgggt tccatgcagt tctccagtgg gacatcagtg cttatccgaa	60
tgtcatcaat ggcaatctct ccggaacgtc ctttccctat cactccctcg aacacaatct	120
ggtaactccat gtcgtagctg ggcaggatga tccgcccgtg ctt	163

<210> SEQ ID NO 108

<211> LENGTH: 267

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

tgcttttcta tgcactttgt ttttttcttt gggctttggt ttttttttcc acttagaaat	60
tgcatttctc gacagaagga ctcagggtgt ctgaagtcac tgcacagtgc atctcagccc	120
acatagtgat ggttcccctg ttcactctac ttagcatgtc cctaccgagt ctcttctcca	180
ctggatggag gaaaaccaag ccgtggcttc ccgctcagcc ctccctgccc ctcccttcaa	240
ccattcccca tgggaaatgt caacaag	267

<210> SEQ ID NO 109

<211> LENGTH: 146

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

gctttgatat ttcaatgtta gcctcaattt ctgaacacca taggtagaat gtaaagcttg	60
tctgatcggt caaagcatga aatggatact tatatggaaa ttctgctcag atagaatgac	120
agtcctgcaa aacagattgt ttgcaa	146

<210> SEQ ID NO 110

<211> LENGTH: 174

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 110

```
gatcagcaaa caggaatacg atgaagccgg gccttccatt gtccaccgca aatgcttcta    60
aaacactttc ctgctcctct ctgtctctag cacacaactg tgaatgtcct gtggaattat    120
gccttcagtt cttttccaaa tcattcctag ccaaagctct gactcgttac ctat        174
```

<210> SEQ ID NO 111

<211> LENGTH: 165

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

```
ctcagggagc gaactgtgat gaaaaccaca gggattccgg acgccagacc ccattttata    60
cttcactttt ctctacagtg ttgttttggt gttgttggtt tttatttttt atactttggc    120
cataccacag agctagattg cccaggtctg ggctgaataa aacaa                    165
```

<210> SEQ ID NO 112

<211> LENGTH: 257

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

```
ttgttactgc tgattcttgt aaatcttttt gcttctactt tcatcttaaa ctaatacgtg    60
ccagatataa ctgtcttggt tcagtgagag acgccctatt tctatgtcat ttttaatgta    120
tctatttgta caattttaaa gttcttattt tagtatacgt ataaatatca gtattctgac    180
atgtaagaaa atgttacggc atcacactta tattttatga acattgtact gttgctttaa    240
tatgagcttc aatataa                    257
```

<210> SEQ ID NO 113

<211> LENGTH: 191

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

```
taggtggtag atattgaggc caagaatatt gcaaaatata tgaagcttca tgcacttaaa    60
gaagtatttt tagaataaga atttgcatac ttacctagtg aaacttttct agaattattt    120
ttcactctaa gtcattgatg tttctctttg attatttgca tggtatgttt aataagctac    180
tagcaaaata a                            191
```

<210> SEQ ID NO 114

<211> LENGTH: 116

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

```
tgctgtgaaa gaggtgggct acacaatcga atggtttgag gtgatctcgc aaagtatttc    60
ttccaccatg gccacaacg aaggactttt ctccctgggt gcgaggaagc tgagca        116
```

<210> SEQ ID NO 115

<211> LENGTH: 227

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

-continued

tatttgaact atatgttgaa gacatctacc agtttctcca aatgcctttt ttaaaactca 60
tcacagaaga ttggtgaaaa tgctgagtat gacacttttc ttcttgcattg catgtcagct 120
acataaacag ttttgtacaa tgaaaattac taatttggtt gacattccat gttaaacatc 180
ggtcattgtc agcttcattg catgtaatgt agacctagtc catcaga 227

<210> SEQ ID NO 116
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

ttgcttttca ttcagatgta tacataaact tattttaaag gtcatttaag tgaaccattc 60
caaggcataa taaaaccoga ggtagcaaat gaaaattaaa gcattttattt tggtagtctt 120
tcaataatga tgcgagaaac tgaattccat ccagtagaag catctccttt tgggtaattc 180
gaacaagtgc caaccagat agcaacatcc actaatccag caccaattcc ttcacaaagt 240
ccttccacag aagaagtgcg atgaatatta attgttgaat tcatttcagg gct 293

<210> SEQ ID NO 117
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

gatgcttaac aaaggttacc ataagccaca aattcat 37

<210> SEQ ID NO 118
<211> LENGTH: 179
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

agaggttata ggctactcct ggggcctctt gggccccca cgtgacagtg cctgggaatg 60
tattattctg cagcatgacc tgtgaccagc actgtctcag ttctacttcc acatagatgt 120
ccctttcttg gccagttatc ccttcctttt agcctagtcc atccaatcct cactgggtg 179

<210> SEQ ID NO 119
<211> LENGTH: 220
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

ctgtatcact gccttcggtt atatcttttt aactgtgata atccccacag gcacattaac 60
tgttgcactt ttgaatgtcc aaaatttata ttttagaaat aataaaaaga aagatactta 120
catgttccca aaacaatggt gtggtgaatg tgtgagaaaa actaacttga tagggcttac 180
caatacaaaa tgtattacga atgccctgt tcatgttttt 220

<210> SEQ ID NO 120
<211> LENGTH: 237
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

acaaaagctc ccctgatcca actagcacac tgtcaaatac agtgtcatat gagaggtcca 60

-continued

cagacggtag tttccaagac cgtttcaggg aattcgagga ttccacctta aaaccttaaca	120
gaaaaaaacc cactgaaaat attatcatag acctggacaa agaggacaag gatttaatat	180
tgacaattac agagagtacc atccttgaaa ttctacctga gctgacatcg gataaaa	237

<210> SEQ ID NO 121
<211> LENGTH: 197
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

agtgctaagg agtatagcag atgacttata tgtgtgttgg ctgggagaat atcatcttaa	60
agtgagagtg atgttgttga gacagttgaa atgtcagtc tagagcctct gtggtgtgaa	120
tgggcacgtt aggttgttgc attagaaagt gactgtttct gacagaaatt ttagctttg	180
tgcaaaactca cccacca	197

<210> SEQ ID NO 122
<211> LENGTH: 131
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

ctacttcccc gaaccggtga cgtgtgtgtg gaactcagcg gccctgacca gcggcgtgca	60
caccttcccg gctgtcctac agtcctcagg actctactcc ctcagcagcg tggtagccgt	120
gccctccagc a	131

<210> SEQ ID NO 123
<211> LENGTH: 95
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

ccagacctac acctgcaacg tagatcacia gccagcaac accaaagtgg acaagacagt	60
tgagcgcaaa tgttgtgtcg agtgcccacc gtgcc	95

<210> SEQ ID NO 124
<211> LENGTH: 131
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

gtaatttgtg attgtcgagg aagaggtgtg gctgttggtg tgatagtaat actgctggtg	60
actttattgg ttgttttgtt tagtgccccg ttaattaagc cttgagttcg gttatcctgc	120
agtggtgctg a	131

<210> SEQ ID NO 125
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

tttccccac tgtctggaca ctggtgaatg acattaga	38
--	----

<210> SEQ ID NO 126
<211> LENGTH: 173

-continued

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

```
gaaggagaac gaatccagtg gaaagaaagc tggtagggga aaagatgcc tgcagaaaag      60
tccccctttcc cccactgtct ggacactggg gaatgacatt agaagagacc cccccattc      120
aagtccccctc actggctcct tttctcccca ctacaccact tccaaaatct gaa          173
```

<210> SEQ ID NO 127

<211> LENGTH: 145

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

```
gataccgact gaccgtgggc cttaccgaa gaggacagcc catgcagtac aatgtgggtc      60
cctctgtctt caagtaccca ctgaggaatc tgcagcctgc atctgagtac accgtattcc      120
tcgtggccat aaagggcaac caaga          145
```

<210> SEQ ID NO 128

<211> LENGTH: 111

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

```
ttaagacatt ggagtgatth ctggaatgt tttctttaag aaggtcacg tgatgtttgt      60
gtttacttgt ggttgcccta tcctatgctg cataaatcct tgaaaggaaa g          111
```

<210> SEQ ID NO 129

<211> LENGTH: 137

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

```
ttaagacatt ggagtgatth ctggaatgt tttctttaag aaggtcacg tgatgtttgt      60
gtttacttgt ggttgcccta tcctatgctg cataaatcct tgaaaggaaa ggttttagtt      120
agttgctttc tttcttc          137
```

<210> SEQ ID NO 130

<211> LENGTH: 156

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

```
ctgagtaaat gggactgctg tcgttgatg gcactgcga gctcaggggt gggctctggg      60
aggcggaggc ggaggaggcc gctggagatg gtgctgagga cgaggaggcc ggtgggttgg      120
tcattgctac taggccactg accaagctga agaggg          156
```

<210> SEQ ID NO 131

<211> LENGTH: 163

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

```
agaattaact gactatggtt ttgcaggcca gtttgatccc agtattttta tttctaaagg      60
ggttcttata gttcctctga ttgttaccat tttaaaatag agaaagtcca tagtgatgcc      120
```

-continued

tttcctttca gtggttgatt ggacgacct cttgagaatg cat 163

<210> SEQ ID NO 132
<211> LENGTH: 269
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

atttgcattt taccatgggt cctcaataaa taaatagaat gttgtttttt gtattttaag 60
tttttttttg tttttccct cagaggaagg atgaaaaaaa gaattaactg actatggttt 120
tgcaggccag tttgatccca gtatttttat ttctaaaggg gttcttatag ttcctctgat 180
tgttaccatt ttaaaataga gaaagtccat agtgatgcct ttcctttcag tggttgattg 240
gcacgacctc ttgagaatgc atgcatgaa 269

<210> SEQ ID NO 133
<211> LENGTH: 105
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

atttccatca catatgtgcc aagacttggt ttctgtatcc aggagtgtgt tagatactaa 60
catagtgttt catttacatg tgtgtgaaac ctgggtgaag agcca 105

<210> SEQ ID NO 134
<211> LENGTH: 174
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

ccatcagttt ttccaatgtg aatggactgg ttcatatcac accatattta gagatacaag 60
gtgattataa ctaacgtgtc tacaagacat actgggtcaa acaatgtgat caatccaaag 120
ggatatcttt taaaaagaat ttaagtactc agctgcaaag ataagttcac taat 174

<210> SEQ ID NO 135
<211> LENGTH: 218
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

gtacatggtc tggagtaacc tttatatgaa gtggtgccc aggtgtgtgg cttaggacta 60
gatctccagg ttgcacaaag ttggcattgg gtttagtttg catttttcca ttctgaagat 120
ggccctcctt ggattttcatc caggaaatcc atagctttct gttaacagga catggagtag 180
actggctgca tttgaaggac agcacagatc cctcatca 218

<210> SEQ ID NO 136
<211> LENGTH: 103
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

aaaccttggt ttattcagcc cagacctggg agatctagct ctgtggtatg gccaaagtat 60
aaaaaataaa aaccaacaac aacaaaacaa cactgtagag aaa 103

-continued

<210> SEQ ID NO 137

<211> LENGTH: 194

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

tcaaactcag gtatgtgaca ctctacagtt caatgctagc acacctgtgt gaggettaac 60

aacatgagga actgatagcc agtgatacac aaatccagca ctccctctcc atttactctg 120

tcaggctgta tatggggagc aacacatatg gctttgtggc agccagaaag tgaaggtcct 180

tttaggaggt gaca 194

<210> SEQ ID NO 138

<211> LENGTH: 268

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

gtaaagcttt ggcacatata gtataaaaaa taatcaccca ccataattat accaaattcc 60

tcttatcaac tgcatactaa gtgttttcaa tacaattttt tccgtataaa aatactggga 120

aaaattgata aataacaggt aagagaaaga tatttctagg caattactag gatcatttgg 180

aaaaagtgg tactgtggat atttaaaata tcacagtaac aagatcatgc ttgttcctac 240

agtattgctgg gccagacact taagtga 268

<210> SEQ ID NO 139

<211> LENGTH: 37

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

tgggctggag ccgcacacgc tctcctocca tgtaaa 37

<210> SEQ ID NO 140

<211> LENGTH: 158

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

ttttcgtagt ccaaaggctt tattgttctg ctgaaatgct taaaactact gaaaaccccc 60

agcctgggcc caggcaacca agggctcaat gctgggaagg agagcagggg aggtgggctt 120

agtgttaagg cgtgaagggc gaggccagac agctggag 158

<210> SEQ ID NO 141

<211> LENGTH: 182

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

tgagtaggtg agtttattgg gacttacaca caggccaatc ctgggcggcg acaagacagc 60

tctagagatc tgagcttctc cccaatgcta aactgcttct atgctaattt tctgactgtt 120

tacttaccgg gtaagagcga tgggactgtt ttcattgggt gggtctcaca tactctctgg 180

ga 182

<210> SEQ ID NO 142

<211> LENGTH: 94

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```

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

gctccatt caagtgaagt tataatttac actgagggtt tcaaaattcg actagaagtg      60
gagatatatt atttatttat gcactgtact gtat                                94

<210> SEQ ID NO 143
<211> LENGTH: 165
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

tttcctgccc caaggcagat ccacatcacc gaagctccct agaggggcaa aagatggagt      60
gagccacagg aagtttgggg cgtggtgagt tggaatgata cgtccatttc tctatgaaat    120
atttgctact agactgttca tttctctctg acatgtttgt tgaat                    165

<210> SEQ ID NO 144
<211> LENGTH: 227
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

agcccaactt cttaccgaa agcatcactg ccttggeccc tccctccgg ctgcccccat      60
cacctctact gtctcctccc tgggctaagc aggggagaag cgggctgggg gtagcctgga    120
tgtgggccaa gtccactgtc ctctctggcg gcaaaagccc attgaagaag aaccagccca    180
gctgcccccc tatcttgtcc tggaatattt ttgggggttg aactcaa                  227

<210> SEQ ID NO 145
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

tattgaggac ccatggtaaa atgcaaatag atccgggtgc taaatgcatt catattt      57

<210> SEQ ID NO 146
<211> LENGTH: 135
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

taccgggaa agtacgtcta gattgtgtgg ttgcctcat tgtgctattt gccactttc      60
cttcctgaa gaaatatctg tgaaccttct ttctgttcag tcctaaaatt cgaaataaag    120
tgagactatg gttca                                                    135

<210> SEQ ID NO 147
<211> LENGTH: 174
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

tgtcatggag acttgaggag ggagggttg aggttggtga ggtaggtgc gtgtttcctg      60
tgcaagtcag gacatcagtc tgattaaagg tgggtccaat ttatttacat taaacttgt    120
cagggtataa aatgacatcc cattaattat attgttaatc aatcacgtgt atag          174

```

-continued

<210> SEQ ID NO 148

<211> LENGTH: 132

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

acagcccacc cttgtgtcca ctgtgacccc tgttcccatg ctgacctgtg ttctctcccc 60

agtcacatctt cttgttccag agagggtggg ctggatgtct ccacatctctgt ctcaacttta 120

cgtgcactga gc 132

<210> SEQ ID NO 149

<211> LENGTH: 173

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

aatgctcct tgaatattaa aagggtgttaa aaatagtcca tggtatgtga ttccaatttt 60

gttttttaaa atatgggtgt atgcttgat acgtagagca gataaaaaag acggaaggca 120

tactaaaaaa tgttgagtgg ttatcttctgt atggtggaac aaagtcactg taa 173

<210> SEQ ID NO 150

<211> LENGTH: 247

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

ggcaggcttc tctgtagaac ccaggggctc tcggcccaga ccacagcgtc ttgccctgag 60

cctagagcag ggagtcacca acttctgcat tcacagacca cctccacaat tgttataacc 120

aaaggcctcc tgttctgtta ttcaacttaa atcaacatgc tatcttggtt tcaactcactt 180

ctgacttttag cctcgtgctg agccgtgtat ccatgcagtc atgttcacgt gctagttacg 240

tttttct 247

<210> SEQ ID NO 151

<211> LENGTH: 112

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

attttagtat ggtgtctgtt tatgtaactc tgacttgctg gaaaagttga aactccaaat 60

aatctgaaac tagaaaagaa atagcacata attactacct tccccttggc gg 112

<210> SEQ ID NO 152

<211> LENGTH: 278

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

aaatggcttc cgatttccag cttgggcctg gggattggag atgtccccc tgagagtagg 60

gcacaagtga ggaatgggtt tggagaggaa gatgataagt tacatcatgg atgtgctgag 120

tctgagttgc ctatgggact tggaatgggg ggtggcaaaa ggtgtgtgat cttgagcaag 180

atattcaact cttctgggac ttggtcttct catttgtaaa acggtgataa gaatattact 240

tcccatttgt gttgctgtga atattaaatg cgctacca 278

-continued

<210> SEQ ID NO 153
<211> LENGTH: 137
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

gtgggcagca cttagattcg gagccatgga tagtccggag tccaaggtct ctgggtgagc	60
agacagtcgg ccaaggcca gcctggagtc aaagagacca gacctgct tagattgcca	120
tactcgacc attccaa	137

<210> SEQ ID NO 154
<211> LENGTH: 252
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

agttcggcaa aggtgtccta gaaatggcca gagtttttga cagacagagt gtagtctcct	60
tattagaaga aaggaaaaaa aagcagaggc caaagaagtt ttgtgtttgc tgatgagagc	120
cccactcatt tgcgaaacgc acgtaaaaca aagtgaaccg tgactgttaa actagggatg	180
ggaaattttg catcttgggg ggctgtacat ttatttattt agttgaagat tcactgatcc	240
cactttgaaa ta	252

<210> SEQ ID NO 155
<211> LENGTH: 106
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

gtgcatgtgt gtgctgtgtc tttgtgtgtg tgetgtgtgc tagtgtgtgt gctgtgtgtg	60
catgtgtgtg cgtgtgtgtg gcgtttgtgt gctgtgtgct cgtgtg	106

<210> SEQ ID NO 156
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

tgggaagcgg cgagatcctc gggctggggg tgcccacgtt tgctacctcc ccctgtgaaa	60
tcgctggtgc tcacaattgt ctttcacagt gtatgtgatt tttttaagga aaaaaaaaaa	120
atccctatth aagatthtga aggtgctacc attatthtgc cacagactth gaagaaactt	180
ttggatgtgg ggcacatccc gcatctttct ctctcctcca aatgacaaa tttggggaat	240
ttttgaatth tcctagcatc gcccttgtgc tcatcaggta atctgctaag gagg	294

<210> SEQ ID NO 157
<211> LENGTH: 238
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

accatcctg ttcgtgaata ggtctcagg gttgggggag ggactgccag atttgacac	60
tatatthttt tttaaattca acttgaagat gtgtatthcc cctgaccttc aaaaaatgtt	120
ccaaggtaag cctcgtaaag gtcacccac catcacaaa gcctccgttt ttaacaacct	180

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ccaacacgat ccatttagag gccaaatgtc attctgcagg tgccttcccg atggatta 238

<210> SEQ ID NO 158
 <211> LENGTH: 258
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

cattctttcc tccacaggat tgctttgtcc atctcctgct ttcatttcaa gtgcataaac 60
 aaaacctcaa agggcctggg aaggtgaggc aggccagagt ctgtgttctg tgttgagtgt 120
 caagctatatt gttaagaagg ttgcaacag gcctttggtg tgggctttgc cagagactgt 180
 tttgaacact ttgcttgaga tccgtgccct gtaaaatgga tatgatgttt tactgatgtc 240
 tgtaatacat ttgtaaac 258

<210> SEQ ID NO 159
 <211> LENGTH: 85
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

ttaagcgcat tagaaaaaa ttgtttgtaa tggaatcaaa gtgtttccct ggacagtttg 60
 atgtgcttat gggtgagatt tataa 85

<210> SEQ ID NO 160
 <211> LENGTH: 299
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (127)..(127)
 <223> OTHER INFORMATION: n is a, c, g, or t
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (194)..(194)
 <223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 160

atttgcaaca gcctagtggg ttggtaggg tcttgaatca tctctataag gcaacaagg 60
 aaattgtaac acaagaaat aaacatattg aatataattg ctattctgta agacatacag 120
 tctgtgnaag atgtatctta ttacagaga catttttgaa aattaaaata ttaaatactt 180
 tttgttatat aganacaatg atctggaagt ataaaaagaa aaatattatc ttgttgatgt 240
 aaatatgata tccttatata tattagaatc caataagata tcatgggcgc aatattagc 299

<210> SEQ ID NO 161
 <211> LENGTH: 229
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

gatggctggg agataagtcc ttgaatggag gaaccaagag gtgagttaga ggcataaact 60
 aaggaatttc agtttagtag gttaggagt gacagtctag aatgagtgga gactaggaga 120
 ttcattcttg tgcaagcata cttagatcca tggtactcag gatagcatag gtgagagagg 180
 agctggtaga attttaatgt catacctggg tagtacaact gggtattat 229

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<210> SEQ ID NO 162
<211> LENGTH: 213
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

tattttccgg ttgacccag aattcattag atttttttaaa aaaacaattt caaaatagtt      60
gctgttttaa attagttgca tccagttcat atcaatgttt gcatgctttt tagtctttgt      120
tatttattga aaacctttgg tacctaaact taagtttgat tgtttcagtg tgtacttggt      180
aaatatgtca gtggcctttt aactaaacat caa                                213

<210> SEQ ID NO 163
<211> LENGTH: 174
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

caccacagga ctttatcaac ttgttcaagt tctgaatccc agcacatgac aacacttcag      60
aaggggtcccc ctgctgactg gagagctggg aatatggcat ttggacactt catttgtaaa      120
tagtgtacat tttaaacatt ggctcgaaac ttcagagata agtcatggag agga          174

<210> SEQ ID NO 164
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

atggacaatt ctgtaccca ataatacagaa ca                                32

<210> SEQ ID NO 165
<211> LENGTH: 166
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (101)..(101)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 165

agagagggtt gtcccatata tcttggtcca gcagccatat atcttggtgt ctacagcctg      60
aagcatgatt tcccttgaag tcttgggggt gtttaaagga nagtcccttc aatataaaac      120
ctctgaaata ttagtgagaa tggtcacta atgtgaacaa tgttta                    166

<210> SEQ ID NO 166
<211> LENGTH: 213
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

tacaaagaat atttggggcc agtgctacag aaaaacatga actacatctt atcgtcacaa      60
aatagccatt ataaaatgaa ttttcagcc tctgtttttt tgaactttga aataaaatgt      120
tcagacaaat attcaacttt ttaaaaacct ccattcattg atagcctgag aaatgtacaa      180
tgaacatggt taggcagact gctagtattt tgc                                213

<210> SEQ ID NO 167
<211> LENGTH: 225

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<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

cctccaccaa tcatactttg acatttatct atttccttct ccacttatgg atgtaattgg	60
cttgctatag aaactacagt tcagatgctt tgaatgtatg aactacaatg aacaataaag	120
tcctcttctt ttgaagcata ttttggttc agctttaaga taatcttatg acaagaagg	180
tcacactgat tcacttaata aattccattc ttacctaaca caagg	225

<210> SEQ ID NO 168

<211> LENGTH: 259

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

gctggtgtgt ggatcggatg ggcaagtccc tgccagggtc tccagatggc aatggaagct	60
cctctgctccc cactgggagt agcggctaaa gctgggggat agaggggctg cagggccact	120
ggaagggaaca tggagctgtc atcactcaac aaaaaaccga ggccctcaat ccaccttcag	180
gccccgcccc atgggcccct caccgctggt tggaaagagt gttggtgttg gctggggtgt	240
caataaagct gtgcttggg	259

<210> SEQ ID NO 169

<211> LENGTH: 217

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

gaccccgatg gaaaacaaag ccaaacaaaa ctgaaccaca aaaaaaggc tgggtgtcac	60
caaaacaaaa cttgttcatt tagataattt gaaaaagttc catagaaaag gcgtgcagta	120
ctaaggggaac aatccatgtg attaatgttt tcattatggt catgtaagaa gcccttatt	180
tttagccata attttgcata ctgaaatcc aataatc	217

<210> SEQ ID NO 170

<211> LENGTH: 243

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

gagtaaaaaag aaccctttgc tgagtaacca agcctttaat tttgtgtttt tatgaaagga	60
attaaaaatc ccacgataaa tatttaccac aacctgtgtc agataaatgg gaaattaaac	120
acagattgta caatgtgagc ttgggagtta atggcccaga ttttactggt aggcagtaag	180
agttggagta ggtagtcttg ttatcatgag aagaaccttg aacagatata actaatttac	240
ata	243

<210> SEQ ID NO 171

<211> LENGTH: 172

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

aacaccata atcaatcaca gagataacca ctgttcataa ttccttcag tcttcttact	60
tggcacatat acatttgtct tcttttatat atgacatat gatattttac aaagtttaga	120

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tcctactcta tgcactgctt ggtgatcgga tctattcaat gtacaaaata tt 172

<210> SEQ ID NO 172
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

ttttctaacc ttgattgacc atgggcaaat gaaactgcag aaagtgaac tgcggatagg 60

ggggatgact gtattcaata gattccgaca ttatgtctgc 100

<210> SEQ ID NO 173
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

ttataatgag tgcgatatat gttgtcgagg ct 32

<210> SEQ ID NO 174
<211> LENGTH: 210
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

gttttgatgc tgtgtgcttt tggctgggcc tcgggctcca ggccctggga ccccttgcca 60

gggagacccc cgaacctttg tgcaggaca cctcctggtc ccctgcacct ttctgttcg 120

gtttagaccc ccaaaactgga gggggcatgg agaaccgtag agcgcaggaa cgggtgggta 180

attttagaga caaaagccaa ttaaagtcca 210

<210> SEQ ID NO 175
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

ttcattgagg ttcgtgtgtg ctgtgttcgc gtgtgtgtgc tgtgtgtgca tgtgtgtgct 60

gtgtcttagt gtgtgtgtg tgtgctagt tgtgtgctgt ggggtaccga gctcg 115

<210> SEQ ID NO 176
<211> LENGTH: 241
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

ttcatcatat ccaagtacac tctgtcttcc tgagcagtgg aagatcatat tgctgtaact 60

tcttttaagt agttgatgtg gaaaacattt taaagtgaat ttgtcaaat gctggttttg 120

tgttttatcc aacttttgtg catatatata aagtatgtca tggcatgggt tgcttaggag 180

ttcagagttc cttcatcatc gaaatagtga ttaagtgatc ccagaacaag gaataactaga 240

g 241

<210> SEQ ID NO 177
<211> LENGTH: 148
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (91)..(93)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 177

gtcattgata cctgtagtaa gttgacaatg tggtgaaatt tcaaaattat atgtaacttc      60
tactagtttt accttctccc ccaagtctnt nnnaactcat gatttttaca cacacaatcc      120
agaacttatt atatagcctc taagtctt                                          148

<210> SEQ ID NO 178
<211> LENGTH: 198
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

gattttcttt tgacacagct ccaaggccac cagctatgca aggccacaag ttatgcacta      60
tatgattaac tgcttttggt ttacttttgt aagtccactt ataaaaaccc tgctctgtct      120
ttgtttaatg ctcagctttt tggatttgaa tccactcagc cgggtgcacac cttaaaaataa      180
acatcctcct gtactctc                                                    198

<210> SEQ ID NO 179
<211> LENGTH: 269
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

agacctagaa gggtgtagat gggaaatcag gaatgatttg aactgataaa gatttcagac      60
tcataagaac acattttata aatgttaaac acaaaaaacta catgactgaa gatagaagag      120
aatgcatggg attttattac acatgggtga agagagaaga ggcgtgtagg ttgcaaaca      180
aagttaagaa ataggaaact gaatttttca ttgtacagaa aatgtatctc ttggggaggg      240
cctgtgtacc ccattctct gattataaa                                          269

<210> SEQ ID NO 180
<211> LENGTH: 243
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

ggattttttc ccctgtagta gtgaggtaac atgcttgaat gtcactgtga tatttatttc      60
ctctttgttc agttgttttt gaattcctgt taagtacatg ttttaatact ttgagcgatt      120
taagatactt ttctttttgc ccatcathtt cccaaggaa tgtaattcac ataaatccaa      180
agctcatttt tttttttatt gtacacaagt agtataatgt ttgcttttcc caataaacct      240
caa                                                                    243

<210> SEQ ID NO 181
<211> LENGTH: 178
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (123)..(123)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 181

gagacaagga cagacaaatt ttctggctgt ccccatctct cctgggggag gggtttgggg      60
ctggtttgac tttaattggt gggngggtn gttctgccgc tctgtttgct gcagtccccg      120
tgnctgtctt ggggactgag aaatttgagc caggtatcca gagccacagc ccatcttg      178

<210> SEQ ID NO 182
<211> LENGTH: 238
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

agttggtgcc ctgattccat ttttctcaag ttgtagaaga acaaaactaa tttacggtag      60
gagaaattca aattcagatt ctcccatcc ccaccagtta ctttggttg gtggagagg      120
ggagaattgg caggaagg gacaaagaa actttttggg gtgatggaaa tattttgtac      180
cttgctttag atgttggtca gatggaatat acgtttgtgg aaacctgcca aactgtac      238

<210> SEQ ID NO 183
<211> LENGTH: 155
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

aaacattacc gggcatggta gcttgacct gcagtccag ctacttggga gactgaggtg      60
agaggatcac ctgagtgtag gaggtgaaag cctcaccgaa ctatgactga accactgcac      120
tccagcgtgg gcacttggca ccagagcaag attct      155

<210> SEQ ID NO 184
<211> LENGTH: 47
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

gggatgcata aagtatgagt gccttttagg atgggaattg agatgta      47

<210> SEQ ID NO 185
<211> LENGTH: 235
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (157)..(157)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 185

aggatttccc aaaccagccg aggccccagc acccgccgtc tcccagaag cccctctctc      60
cttcccccat gggcatatg ttgaaagtct attttaaaaa ctatgttcct tgccgtagat      120
tgcagagcta atttatcag tttctctcct gtgaganccc cccttttata tgatatatcc      180

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agaggaagtt ttgtaatata aaacaggacg cccacactga tggttttgca ctggt 235

<210> SEQ ID NO 186
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

tttgatttg aatccactca gccggtgcac accttaaa 38

<210> SEQ ID NO 187
<211> LENGTH: 265
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

tgttttagaa ccagccgtat ttacatgaa gctgtataat taattgtcat tatttttgtt 60

agcaaagatt aaatgtgtca ttggaagcca tccctttttt tacatttcat acaacagaaa 120

ccagaaaagc aatactgttt ccattttaag gatatgatta atattattaa tataataatg 180

atgatgatga tgatgaaaac taaggatttt tcaagagatc tttctttcca aaacattttt 240

ggacagtacc tgattgtatt ttttt 265

<210> SEQ ID NO 188
<211> LENGTH: 56
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

cacaatctga gcacgctacc aaatctcaaa ataccctaag actaacaag gcagct 56

<210> SEQ ID NO 189
<211> LENGTH: 289
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

tcccaagtag tgctgactga ctctcctggt gacaggggtt tgtgtccgag cccctgcggt 60

caaggagtgt ggagcaaac gtgggtacta ggggtggagg cggggaaagg ccacagcaca 120

ctggcgctcc agcaagcca aatcatgtct cctctggcca ctgcggtcct ctcttggtta 180

catgtcatcc ccagaggag tatccaaagc tattccacta tgcactcatc aaccctggct 240

tgtcagcctt ggggaaggtc actttattca taaaaatgcc tctttgagt 289

<210> SEQ ID NO 190
<211> LENGTH: 212
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

cctgagtcct gggatcagac accccttcac gtgtatcccc acacaaatgc aagctcacca 60

aggtccctt tcagtcctt tcctacacc ctgaccggcc actgccgcac acccaccag 120

agcacgccac ccgccatggg agtgtgtctca ggagtcgagg gcagcgtgga catctgtccc 180

agagggggca gaatctccaa tagaggactg ag 212

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<210> SEQ ID NO 191
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

cagggttcct ttgctgcta acaagccac gtggaccagt ttgaatgtct ttcctttaca      60
cctatgtttt taagtagtca aacttcaaga aacaatttaa acaagttttt gttgcatatg    120
tgtttgtgaa cttgtatttg tatttagtag gcttctatat tgcatttaac ttgtttttgt    180
aactcctgat ttttcctttt cggatactat tgatgaataa agaaattaaa gtgatagttt    240
tattggtttc ctttcccca attaaggcca aataaagtcg tgagaacatt accc          294

<210> SEQ ID NO 192
<211> LENGTH: 52
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

gaggccggtg ccagtgcagg tccttgggtg gctgtgtgcc ggccccctgg gc          52

<210> SEQ ID NO 193
<211> LENGTH: 297
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

atggtaatgt aggatccttt cacagagtgc caggctaaag agctgaactt tgtgggtggaa    60
gagacagacc ccctatgtgc tctgtagaca cctgtgatga agtagaactc atgaggatat    120
gaagagaaac atttgaatt tgagtgatta aactaggaac gaaagaggag gggagaaata    180
ggaagagaga atcacccgcc ctgttgactg atttgagctg ggaatgaaga agaaaaccct    240
gcaggtgtgg gcaccaatgt ttgaaacccc cacagtgtga gtctcaactc tgtgtgta    297

<210> SEQ ID NO 194
<211> LENGTH: 223
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

ccatgtcagc ctggatagag gtatatgacg tgtgccaaaga atttatccca gactccccctg    60
tgtgacagct tcataataaa gttacttaac tgtgcctctt cctccttctt ctccccacac    120
aggatggatg ggcattcttc tccttgacca ccctactctc ccttcctccc ctgatcacct    180
ccccctcctg ctctccccctg gtgatggact tctaacatga gat          223

<210> SEQ ID NO 195
<211> LENGTH: 238
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

actggtatat tattgcttca tgtttgttac catcataaga ttttgtgcag atttttttta    60
cagaaattat ttttttttat gacaatatga cacttgtaaa ttgttgtttc aaaatgaaca    120
gcgaagcctt aactttaaat gacatttgta ttttcagaca ctgagtagca taaaaaccac    180
atagaactga actgtaactt aaattccaaa ctatgactac tacattccaa agaaacag    238

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<210> SEQ ID NO 196
<211> LENGTH: 129
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

```
cgtccccaac atgcattctca ctctgggtgt ctggtctttt tattttttgt aagtgtcatt    60
tgtataactc taaacgcca tgatagtagc ttcaaaactgg aaatagcgaa ataaaataac    120
tcagtctgc                                     129
```

<210> SEQ ID NO 197
<211> LENGTH: 277
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

```
tggaggattc aagatgagca ggtatgtttt ctgctttcaa taactcattt tctgctgcag    60
agatagcctt gtaagcaagc aaaggaaaac ttgacattt ctctgcaaag ataatgcatt    120
acatataagg gtgtgtctgg gagggtagca ggtgcctgtc agcaaaagtt gcaaaaacag    180
cttgataagg gtattaagtg ggctgttg gaaaggcagg agtgtcaaat gtcggacaga    240
actccagaca gagaaatcca gatatccagt aggttag                                     277
```

<210> SEQ ID NO 198
<211> LENGTH: 231
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (92)..(92)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (105)..(105)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (160)..(160)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (169)..(170)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (172)..(176)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (178)..(180)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (182)..(182)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (186)..(187)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 198

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gaatggcaaa acacaaatgg caacataaat gtccatttga cttacctaac ttcacaaatt    60
tcaagttgag gatgtcattt attcttgaat tntgtttttt tactnagatg ctttcaatta    120
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 atagccctat atttttgtgc aggcgaactg tataacaggn ataaaaaann annnnnannn 180

antgannagg aggagaaatt ctcacagaac accatatgag cttagacca a 231

<210> SEQ ID NO 199

<211> LENGTH: 262

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

gagggtgtgat ttttaaggcat tggtatatatt ttttttattt gtgagtgttt taaaattttg 60

tatttctttt aaacttttta ttttagaaaa atttccaaca tatatagaag tagactattg 120

taaggaaccc ttatgtaccc tccaccagct tcaacaacta tcaacaaaag ttgatcttg 180

ttttaaccac attcctttcc aattttttgtg tttaccccca gattattttg aagcaaattc 240

ctgacctcat aacattttca aa 262

<210> SEQ ID NO 200

<211> LENGTH: 187

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

ttcagtttgt cctcataggg aatcaagtat tttagctagg tgatgtcttg caagtacgtt 60

ccactttgtt acaatctact atctgtatat actatttgta tcttaattct tttatgagat 120

gttctgtaac atttttctca ctttgacaaa tgtttttaga ctgtacagtc aagatctggc 180

gcttggg 187

<210> SEQ ID NO 201

<211> LENGTH: 180

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

acagtgatcc cccacgtgtg ttcactctga cccaccgagc caggcagagg ccagccctcc 60

gtggtgcaca cagcacgcgc ctcagtcacat cccatttttag tctttaaac ctcaggaagt 120

cacagtctcc ggacaccaca ccacatgagc ccaacaggtc cacgatggat ccaccagtcc 180

<210> SEQ ID NO 202

<211> LENGTH: 55

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

cagatcgaca cgcagctagc ctccctgcatt gtatgggtat aaatagcacc ctagt 55

<210> SEQ ID NO 203

<211> LENGTH: 207

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

aagtgttcta caaaagaatc cctgtgggta gcttactctt aggttagatc ttetaataag 60

gctgaaattc aaaatcaaaa ccttagtgtg tccgagtcca gcttgggttc cagcattctg 120

ttcaggccac ttctgaacgg ccgaaggtgc cccattccag acctgcccac ttgatggaca 180

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gagcagacag cccggaacag attcaag 207

<210> SEQ ID NO 204
 <211> LENGTH: 241
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (93)..(93)
 <223> OTHER INFORMATION: n is a, c, g, or t
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (97)..(97)
 <223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 204

taagaattta tgaactggg caagttattt cctgggactc aatggtaaag acacagcagt	60
aatccaaatt ttccatcttt gaaattttcc atncttncag tcaatattag taatacctgg	120
gtcaaagggg agagtttagc ataccaatta atgatcatca gaaatgacat agtcctacaa	180
aagcaaagaa aatttagaga cactttctta aaaatacgac tcttggtact gttgaagaaa	240
a	241

<210> SEQ ID NO 205
 <211> LENGTH: 261
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

agccgctgcc aagtctgtat gagaagaaca taatgaagcc tgactcagct aatgtcacia	60
catggtgcta cttcttcttc tttttgttaa cagcaacgaa ccctagaaat atatcctgtg	120
tacctcactg tccaatatga aaaccgtaaa gtgccttata ggaatttgcg taactaacac	180
accctgcttc attgacctct acttgctgaa ggagaaaaag acagcgataa gctttcaata	240
gtggcatacc aatggcact t	261

<210> SEQ ID NO 206
 <211> LENGTH: 274
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

ggttgagttt gtccattgct agggagagac ttccagtaat aaaatttact attctagatg	60
cttctactgt tatgttttat ctgccattt atctttctta gttaccagga gaaatgtgtg	120
acacctatat tataatgaaa acaatcttat tacttatagt ttatctatat taaacaaatt	180
taattgcatt ttaaagcatt ctttgatatt gttgcttttg caataaatat ggataatctt	240
ggttataagg gagttaaaac aatgctgtaa taaa	274

<210> SEQ ID NO 207
 <211> LENGTH: 179
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

tcatggaatg ctacatgctt tctgtttttt tcattttgga tttctccaaa actaactgaa	60
tttaagcttc aggtcccttt gtatgcagta gaaaggaatt attaaaaaca ccaccaaga	120

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aaataaatat atcctacttg aaatttactt tatggactta cccactgcta gaataaatg 179

<210> SEQ ID NO 208

<211> LENGTH: 249

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

cggttgttaa aactggttta gcacaattta tattttccct ctcttgctt ttttatttg 60

aataaaagggt attgagccat tttttaaatg acatttttga taaattatgt ttgtactagt 120

tgatgaagga gtttttttta acctgtttat ataattttgc agcagaagcc aaattttttg 180

tatattaaag caccaaattc atgtacagca tgcacacgg atcaatagac tgtacttatt 240

ttccaataa 249

<210> SEQ ID NO 209

<211> LENGTH: 64

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 209

ccatgaagga gcaagttttg tatttgtgac ctcagctttg ggaataaagg atcttttgaa 60

ggcc 64

<210> SEQ ID NO 210

<211> LENGTH: 57

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

atgaggcaga atctggttgg gtatgtttct tatatatgtt tgaagcagat ggctgac 57

<210> SEQ ID NO 211

<211> LENGTH: 141

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211

atttttgcct ttccgtttct gtctatgatg taggcttctg aggagaacca agaagcttgg 60

ctttagtgggt agaatgacag aacttaggga tcccttgacg gctagaacaa agttctgacc 120

cttagaccaa atctttatgt t 141

<210> SEQ ID NO 212

<211> LENGTH: 108

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 212

gaggaggtgg gcctcgtag actgctcaga ttactggaac ctcgttatca catccattc 60

tacaagtttt tcaactgaatg tttcctgaca tctataaatg agggtgcc 108

<210> SEQ ID NO 213

<211> LENGTH: 158

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213

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gttcaaatga tctacactta ctttttgcaa atcttttttt ttaaattttt taaattttat	60
attttttttc cagccaactc aaggccaaaa aaaattttctt aatatagtta ttatgcgagg	120
ggaggggaag caaaggagca caggtagtcc acagaata	158

<210> SEQ ID NO 214
 <211> LENGTH: 157
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

aggtgggttt gataacacac ttataaggct ttctgtaaaa ggtactatag aaggcggaag	60
aatcgttcaa ctgtcaatca gcctcttgat tctttgtaaa ttgccagggt ggggtgggtac	120
atatctcttc ttgattctgc atttcatact taactat	157

<210> SEQ ID NO 215
 <211> LENGTH: 273
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

gactgagtga gtaactgcaa gctacagggg gcagcttacg tatggcacac aggggtggggc	60
tagcttggtt tcataggctc tctgtggatt ggatgattta aataattttg gtgggacctg	120
gggtttaggg actgtcccta gttgttttgt gctaggtccc agggcagatt agggcagatg	180
tgagtgtgag agcatgataa ggaaagtctt caaggtgtgg aattactcaa ctgctggaga	240
aagggaattt atcagccttt agccagggcc tca	273

<210> SEQ ID NO 216
 <211> LENGTH: 257
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216

gaaagcctga gtttgcaacc agttgtaggg tttttgtgtg gttttttttt tttttttgaa	60
ataaaactat aatataaatt ctctatttaa ataaaattat tttaagtttt agtgtcaaaa	120
gtgagatgct gagagtaggt gataatgtat attttacaga gtgggggttg gcaggatggt	180
gacattgaac atgattgctc tctgtctctt ttttcagctt atgggtattt atcttctatt	240
agtatttgta tcttcag	257

<210> SEQ ID NO 217
 <211> LENGTH: 268
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

atgagtcaaa atccgctctc catgcttact cttgaccccc cattgaagcc actcattgtg	60
tgtgcgtctg ggtgtgaagt ccagctccgt gtggctcctg gcttgactcg ccctgctttg	120
cagttccttt gcacttactc atcgagtgtc gttttgaaat gctgacatta tataaacgta	180
aaagaaaatg taaaaaaaaa aaaccacac acaacaaac ccatacgatc tgtatttgta	240
tatacacgtg tccgtacaag tataacta	268

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<210> SEQ ID NO 218
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218
gaccaaattgg attagactgt aaactgcaaa gtgctgtccg cacatgaggt catctgatta      60
ctgtcctcag atctcttttg tagaggattt caatgtattt ctttaccatt tgagtgtgtg      120
tgtgatggac gaatatgtgt gtgagtttga gaagcatatc gttcgtgtcc agttactttg      180
caaattttgtg gacattttgtg attggacaga ggggtttgtg ctgtggccta acacttgcca      240
agtgaggtgt aggttatgcc tatatgcaaa ttaaacttca cttttcttga      290

<210> SEQ ID NO 219
<211> LENGTH: 205
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219
cctttctaag gatgagggaa tccacaacag actttctcta gaaaaccta atgatggaca      60
acttttttgt gtcacaaatg agttggctac taccttgatg taaaaatttg taaggaaaat      120
tttcaccatt tcgagtgtca agtgtatttt taactgtctg gtttgtaact ttatgacttt      180
tgtactacca aagcggaggt aaaaaa      205

<210> SEQ ID NO 220
<211> LENGTH: 278
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220
ctatcaggtg ctgtgctcat ctgaacaaca aacctcaaca acacgcaatt tatccatgta      60
attaacctgc acatgtaccc ccgaaacctt aaataaaagt tcaaaaaaaaa cctgtgggtat      120
ttaaataggt attgtgtcta aaaatgcatt ctatctaaaa atgtagtttt attgcaactgt      180
ataagaatac gagaggttta aaatagacac tctaaaagtt ataagcccta atttacatat      240
attctctagc ctttctccac cttctatcta ccaaaaaa      278

<210> SEQ ID NO 221
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 221
tcctcatggt ggcagcgctc atagcgaaag cctactgtaa t      41

<210> SEQ ID NO 222
<211> LENGTH: 133
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222
aatgcagaat attcctctga acacttcctt catacatcat tcaatattat aaattaaaca      60
caaagagcct ctccacttag atttttatca tgcacacctac attgtaattgt ctttactctt      120
ccatagaaaa ggt      133

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<210> SEQ ID NO 223
 <211> LENGTH: 74
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 223

 ggtgcaatta ttatactgcg aaaatgaaaa tattgcatac taaacagtac ctagggtatg 60
 atctcaatgt aaaa 74

<210> SEQ ID NO 224
 <211> LENGTH: 172
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 224

 aactgtgacc gtttctgtgt gaagattttt agctgtattt gtggtctctg tatttatatt 60
 tatgttttagc accgtcagtg ttcctatcca atttcaaaaa aggaaaaaaaa agagggaaaa 120
 ttacaaaaag agagaaaaaa agtgaatgac gtttgtttag ccagtaggag aa 172

<210> SEQ ID NO 225
 <211> LENGTH: 258
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 225

 actcaaggct gtgaacaaac atacgtgctt ttattctttc caatttttct cttgttttct 60
 agaactctta tccatagtgt tttaaaataa gtacctaaaa gtggtttgat agtgcctaa 120
 acgacttttt taacttcta aatggaaaga gcataacaat gtagttgatt ggtaagattt 180
 acagggattt ggtttctgag tttgaggcac attcccagtg aataagctga gtcccatacc 240
 acactcaaaa ggttttaa 258

<210> SEQ ID NO 226
 <211> LENGTH: 103
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 226

 attaaagtac tcaagttagt tgttttgag agatgttgcc ttcagatggt aatcaggtct 60
 ctcaagtttc atggagtcta tgctgaccc ttaattgaca aat 103

<210> SEQ ID NO 227
 <211> LENGTH: 258
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 227

 ggatgaagtg gcacacactc taactgaaag cagagtatta aagaacacta gacatccctt 60
 tttaacatcc ttgaaatatt ccttcagac aaaagaccgt ttgtgttttg tgatggaata 120
 tgttaatggg ggcgagctgt ttttccattt gtcgagagag cgggtgttct ctgaggaccg 180
 cacacgtttc tatggtgcag aaattgtctc tgccttgac tatctacatt ccggaaagat 240
 tgtgtaccgt gatetcaa 258

<210> SEQ ID NO 228
 <211> LENGTH: 252

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

ggttctgtaa ggtctttatt tcccataagt aaatattgcc atgggagggg ggtggaggtg 60
gcaaggaagg ggtgaagtgc tagtatgcaa gtgggcagca attatTTTTg tgtaaatcag 120
cagtacaatt tgatcgttgg catggttaaa aaatggaata taagattagc tgttttgtat 180
tttgatgacc aattacgctg tattttaaca cgatgtatgt ctgttttTgt ggtgctctag 240
tggtaaataa at 252

<210> SEQ ID NO 229
<211> LENGTH: 210
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

tttcaagatc ttttgctcac aattcactgc aactgagggg atgtgaatat cattatgcaa 60
taaattaaga gccacagttg gctgaggtga tatgaaagcc aacctgccta aggggggtat 120
gaaagatgtg tatctttcca aacttttaaa acaacgtaag tctgagataa gaacatattt 180
gatggcactg tttggaaaga ggtgctccta 210

<210> SEQ ID NO 230
<211> LENGTH: 258
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 230

ctcaccagga ctctgtctctc cattcccgtc agagtttTgt ttgatttccc ttctctttcc 60
ttctcgggga ccagttctta ctctctttta tttttagett tgcactccat gtggtttcag 120
ggttcagttt gatccatcaa aaggttcttt ttttataatc ctttttgaaa atgataatca 180
aaggaagaga tgtggtgttt ggtcatgtgg aaaactcaat gtataattta gacgtctgtc 240
aaaaatccga caaataaa 258

<210> SEQ ID NO 231
<211> LENGTH: 218
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 231

gtttcaattg attcacaact ttaaaaaata tccacagagg cgtaagagga gatattgtat 60
tgcacccacg aaccagtttt atgctgttta agaaaggac attcaagaaa caaaaaggga 120
gctttgggaa atttgaacaa taaataatag tagaataaaa aattcagaga aagtttggat 180
gataaatttg agccaatctc ccagtaagca gagcaaaa 218

<210> SEQ ID NO 232
<211> LENGTH: 267
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

atgactgtgc tagagccacc ctctcacttt agcctcctga gtagctggga ctacaggtgc 60
ttcccactgt gcctggccaa ttaacaattt catttttatt tttagtagag atgagatctc 120

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actatgttgc ccaggctggt cctgaactcc tgagctcaag agatcctccc acettggcct	180
cccaaagtac tgggattaca aacaagagcc actgtgcctg accaggctct aagattgcta	240
atctggctat agaaggacta atgttag	267

<210> SEQ ID NO 233
 <211> LENGTH: 230
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

aagccgaggg gcccgagact ctgcagcggg gccagaaaga gaagagtggg ggaggaggcc	60
gggagtgggt catggaccag ggggtagagg gaggtgggtg tggacctggg gtcgggcgcc	120
agtcagcttg cagcctatga aggacggaag ggagggtac agagataggg gaagagtggg	180
gctgaggata gccagagcgg cttggcacac agttttaggg taaaagcatc	230

<210> SEQ ID NO 234
 <211> LENGTH: 196
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

tttatttata ccaagctcc tctgaaatt tctcttctt tctttctacc taccgaagac	60
ataccacgtg cttcaataac cagtcccttc ctccacaaa cactacaacc tggaaagcac	120
tcttgctttt ctgaagtct ctatacttag tgtaactctt ctgtgatgaa gattaaagt	180
tattatggca actctc	196

<210> SEQ ID NO 235
 <211> LENGTH: 267
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

aggcattata tatactacac agagtacaat taaaccataa ttgggaatta tattttgttt	60
ttttcttccc aggcaataca cctctgaaca tgtgtgtgat aaatgggttt gctaattgtc	120
tgttttaaag tataaagcat aatatgtttt ggtaacaca atgtactttt tgaactataa	180
atctttatct taatatggaa atgtttggaa caggagatgc aagccactaa cagagaactt	240
taataattct accctgtatt ttataaa	267

<210> SEQ ID NO 236
 <211> LENGTH: 280
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

accacacatt aaactaaagg ctaagaatat aggcttgatg ggaaattgaa ggtaggetga	60
gtattgggaa tccaaattga attttgatc tccttggcag tgaactactt tgaagaagt	120
gtcaatgggt tgttgctgcc atgagcatgt acaacctttg gagctagaag ctctcagga	180
aagccagttc tccaagtttt taacctgtgg cactgaaagg aatgttgagt tacctcttca	240
tgtttttagac agcaaaccct atccattaaa gtacttgta	280

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<210> SEQ ID NO 237
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

acatgagtat ggaatggtgt tttattatga ctttagtttg cattttcctc aattctcggt      60
aaatccttca tt                                                                72

<210> SEQ ID NO 238
<211> LENGTH: 260
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

gagtaggttc ggtctgaaag gtgtggcctt tatatttgat ccacacacgt tggctctttaa      60
accgtgctga gcagaaaaca aaacagggtta agaagagccg ggtggcagct gacagaggaa     120
gccgtctcaa taccttcaca ataaatagtg gcaatatata tatagtttaa gaaggtctct      180
catttggcat cgtttaattt atatgttatg ttctaagcac agctctcttc tctatatttc      240
atcctgcaag caactcaaaa                                                       260

<210> SEQ ID NO 239
<211> LENGTH: 222
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 239

atgattatag aagcgtgtct tagtgcaaaa aacatactta catttcagac atatccaaag      60
ggaatactca cattttgtta agaagttgaa ctatgactgg agtaaaccat gtattccctt     120
atcttttact tttttcttgt gacatttatg tctcatgtaa ttgcatcatt tctgggtggat     180
tgttctagta ctgtattggg cttcttcggt aatagattat tt                            222

<210> SEQ ID NO 240
<211> LENGTH: 216
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 240

gcaatatatt tgtgattccc catgtaattc ttcaatgta aacagtgcag tctcttttcg      60
aaagctaaga tgacctgcg ccttttcttc tgtacatata cccttaagaa cgtccccctcc     120
acacactgcc cccagtgata tgccgcattg tactgctgtg ttatatgcta tgtacatgtc     180
agaaaccatt agcattgcat gcaggtttca tattct                                    216

<210> SEQ ID NO 241
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241

ttggatagca gctatcttgt tggatgtgag gtgga                                    35

<210> SEQ ID NO 242
<211> LENGTH: 258
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 242

atgaaagggtg gaagttctac ctagatttga atgagtgttt ttttaaggga atgagaatgt	60
catggtgcta aacctgacaa ataagagatc attgaaatgc tgaaaatttt aacagttttt	120
ttaaaagtat tgagggggca aaaattacca attatggtat acaaaaataa gcctataaat	180
gtgtttcaca ttgctaactt gagtttcagt tgattcagtt tgtaataact agtaatgagc	240
ttctgtttac aataaaaa	258

<210> SEQ ID NO 243

<211> LENGTH: 275

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (195)..(195)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 243

ccacagtgtt cccactaatg ctatttttta attttttaat ttagtttgtc ataatttgg	60
ttcatcaact cctttgtttt ttccttcttt ttttttttt gagatgaggt ctcactatct	120
tgcccagact ggtttcgaaat tgccctccag caattctccc acctcagcct tcagagtagc	180
tggcattgtg ggtangcacc actgtgccca gctcctgttt tataataaat aagccagagc	240
tctatctcca aatggtgcaa atcatcaatg ctatt	275

<210> SEQ ID NO 244

<211> LENGTH: 281

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244

gggcccctgg tatatatagg gtccaagagg aggcacctgc ttttcaactg caccctcagt	60
gtgcctctt caccggccct aaacgtttcc ctttgaggtt gtgatgctgg gaatcacaga	120
cttcactctc tgctgcacc ctccccgag gtctcatctt ttctgggtcc cacatctttg	180
taataatgtg aaaaagcaca atttgtctga tcacccccca ggtgggtccc caccttatta	240
tcactacctg atccgagtta ctgcaataag tacggtgtcg c	281

<210> SEQ ID NO 245

<211> LENGTH: 274

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245

tgctcagtgt catgctgtgt gtgcatgtgt gtgctgtgtg ttttgtgtgt gtgctgtgtt	60
catgtgtgct gtgcatgcgt gtgtgctgtg tgtgcctgtg tgtgcgggtg gctgtgtcct	120
tgtgtgtgct gtgtgtgcgt gtgctgtgtg catgtgtgtg ctgtgttatg tcgtgtgtgc	180
agtgtgtgct gtgtccgatg tgtgctgtgt acacatgaga gagcagagtg tacatgtgtg	240
tgctgagtct atcagaagat gtgtgtagct gcgg	274

<210> SEQ ID NO 246

<211> LENGTH: 89

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 246

tgtgcccagc ctaagccatt tcttaaaata aaaatgctaa aggactagta agtaaaaata	60
aaacttccta tgggatttcc cagtggaaa	89

<210> SEQ ID NO 247

<211> LENGTH: 72

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 247

gggagattgg tggcccttgc caggaagtgt cttaacactt tgtggatact gctgcctgtt	60
gtcttttaaaa gc	72

<210> SEQ ID NO 248

<211> LENGTH: 177

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

gataacagtc ttgcatgttt atcatgttac aatttaatat tccatcctgc ccaacccttc	60
ctttcccatc ctcaaaaaag ggccatttta tgatgcattg cacaccctct ggggaaattg	120
atcttttaaat ttgagacag tataaggaaa atctggttgg tgtcttaca gtgagct	177

<210> SEQ ID NO 249

<211> LENGTH: 117

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

ttaaacagtc tagagtgaag ggaatgtttt aaaatccaga ggcatcaag tgaagccaac	60
ctttggaggc ccgtagaagt catttggagg aatttggact tcgtgcagta ggaaaga	117

<210> SEQ ID NO 250

<211> LENGTH: 164

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

caggggggcc tgagagtaac agtgaggatt atccagggtc cctgagtgtg acagtgagga	60
ttatccaggg gggccctgag tgtaacagcg aggattatcc agggggccct gagtgaaca	120
gtgaggatta tccagggggg cctgagtgtg acagtgagga ttat	164

<210> SEQ ID NO 251

<211> LENGTH: 259

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (139)..(139)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 251

caaaaatgag tcacaactct tgattccatc cacctccaaa atccaggat tttccttaat	60
tctcattctt tcacaactcc acatatatcc atatcctcat tatctcagga caacgtgacc	120
atttcttgcc acttcccanc acttccatgc ctaccaaaga agcctatctt ctctcaccag	180

-continued

gaccactgaa aaagtcttgc aactgatttc ccttgctctc ttcttgcttc tctacagtca 240

attctctata caacagtca 259

<210> SEQ ID NO 252

<211> LENGTH: 104

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

tgctgcggtc gcctctctca ggctcccccg cteccccggg cctccgcttc tcagccgggt 60

gctgtgcggt tgagtgtgtg ctgctgctcg ctgtgtgtgc tgtg 104

<210> SEQ ID NO 253

<211> LENGTH: 147

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 253

tatatacatg gtgtctcaata gcaacatctt agcagatgaa gcagtttatg attccactcc 60

ctcctgtatg acaggtagcc actatactga atcaagggtc tgaactcaaa tcacaaaatt 120

ctggcttacc gatacaacaa ccaatac 147

<210> SEQ ID NO 254

<211> LENGTH: 208

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 254

ctctgagttt tatatgctgg aatccaatgc agagttggtt tgggactgtg atcaagacac 60

cttttattaa taaagaagag acacaggtgt agatatgtat atacaaaaag atgtacggtc 120

tgcccaaaac accttcccag cctttatgca aaaaaagggg agaatcaaag ctttcatttc 180

agaaatgttg cgtggaaaag tatctgta 208

<210> SEQ ID NO 255

<211> LENGTH: 139

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 255

aaaaagagag aatatgtctc gtgttagctt gcttaggaaa taaagagaga gagagagagg 60

gagggagggg aagagagaaa gagagagaga gaaagagagt gagagaaaga gagagcaaga 120

gagcaagagt aagaagaa 139

<210> SEQ ID NO 256

<211> LENGTH: 243

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 256

ggcagtagat agtcaaagtc aaatcatttc taatgtttta aaaatgtgct ggtcattttc 60

tttgaaattg acttaactat ttctcttga agagtctgta gcacagaaac agtaaaaaat 120

ttaacttcat gacctaatgt aaaaaagagt gtttgaaggt ttacacaggt ccaggccttg 180

ctttgttacc attctgatgt tggactaatt gactaatcac ctacttatca gacaggaaac 240

-continued

 ttg 243

<210> SEQ ID NO 257
 <211> LENGTH: 298
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 257

```

agaggcccat gccaacagtc taatctaaga gattagtctt tcaaactcac catccagttg    60
cctgttacag aataactctt cttaactaaa aacctagtca aacaaggaag ctgtagggtga    120
ggagatctgt ataataattct aatttaagta agtttgagtt tagtcaactgc aaatttgact    180
gtgactttta tctaaattac tatgtaaaca aaaagtagat agtttcactt tttaaaaaat    240
ccattactgt ttgcatcttc aaaagttgga ttaaagggtt gtaactgact acagcatg    298
  
```

<210> SEQ ID NO 258
 <211> LENGTH: 193
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 258

```

agagggaact gtgcagtcgc caggccgcgc cggtccggg ctagaggcaa taaataaacc    60
cgatcctgcc gggcacagcc gcgcccgcgc ctccggcgcc gtccccgggc tgacggggga    120
gggagcggag aagcgagcgc agattctgcg tataaatcag ctctggagca gacacagccc    180
ggctgtgaaa agc    193
  
```

<210> SEQ ID NO 259
 <211> LENGTH: 275
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 259

```

gtaggttttg gagtataacg gtcaccagc gaggggggtga agacggagaa gacttacata    60
gcacggctcag gttagggtcg gacagatgag gaagagctag caaagggggc ttgaggagca    120
gtggccacta agacaggagt gtgacatttt agaagccaaa agaagaccat gtaattcaag    180
ggagagggtat gatttgctgg gtcagatcta aaaataaatc acacgttttt ttaaactgta    240
gtaattaacc actgaaaact tatgagtgat ccaat    275
  
```

<210> SEQ ID NO 260
 <211> LENGTH: 143
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 260

```

gtgtgagcca ctgctggcta atttttgat ttccagtaga gacggggctt caccatattg    60
gccaggctgg tcttgaactc ctccctcgc tccccaaaa atttgaattt ttttttcaac    120
acttttacac ctgttatgga aaa    143
  
```

<210> SEQ ID NO 261
 <211> LENGTH: 263
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261

-continued

```

gagatcactt ggtaactggt ttcattgtga tccaaaaatc agcatttgga tttaagcttt      60
ctgaatttgg tagtttaaga aacagattta gtttttcagt ggttttaact catgtgaaat      120
aatgatatttc caccagcttt gatgcaaaga gatataattt taatgaacga tttatccagc      180
agtttggtcc agggggtgcc tctccttatt tacggggatt actttgtaca tgcagataag      240
ttttcgcaaa cctatttcca ttt                                              263

```

```

<210> SEQ ID NO 262
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 262

```

```

gatgataatc tttactggtg aaaaggatgg aaaaataaat caacaaatgc aaccagtttg      60
tgagaaaaaa aaaaaaaagc cgaaaaaaa aaaaaaaca cctgaatgcg gaagagctcg      120
gtccccgttt agcattttgt acttaaggaa ataaaaaacc aacaaaggat ctcacatttt      180
cttaaaaagt gaagattgct gtatactatt tattcaactt ataatttatg ttactccttg      240
atctttgtct tttgtcatga caaagcattt atttaataaa gttatgcatt cagttcccaa      300

```

```

<210> SEQ ID NO 263
<211> LENGTH: 238
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 263

```

```

agaattccag ataacacac agcctttccc ataccttttt tttcttact ataaaatatt      60
ataagatcca ttgatgtcca aataatacca ccgagcatct cttcacctct cctcctcttg      120
gtccacttgc taatgccccag tttctttctc catttccact tttcttagg ctccttattt      180
actattcatt ttgacttctt tctgttttat ttttttccct ttagcattgc atgtgaat      238

```

```

<210> SEQ ID NO 264
<211> LENGTH: 101
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 264

```

```

tgagtgtgct gtgctcgctg gtgtgctgtg ttcattgcgtg tgctgtgtgt tgtgtgtgtg      60
tagctgcggg gatgcataaa gtatgagtgc ttttttaggat g                          101

```

```

<210> SEQ ID NO 265
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 265

```

```

tttatgaaca gcagactcta tgtaaaggca tttt                                  34

```

```

<210> SEQ ID NO 266
<211> LENGTH: 168
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 266

```

```

aggagggaaa ataatagccc agtgagagct gaatgaaaag ggactgaatt taaatatttg      60

```

-continued

taagaacttt gtgatgatga gtaattgtca gacgtgggat agataactga gaggtcaga 120

atctttacca aggatatttt ttaggataag gtagctgcct gttcatga 168

<210> SEQ ID NO 267

<211> LENGTH: 150

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

agggaccag taagacaaa ggaggggagg acagagcatg aaaacaaaa tccatgcaaa 60

tgaaatgtaa ttggcacgac cctcaccccc aaatcttaca tctcaattcc catcctaaaa 120

agcactcata ctttatgcat ccccgagct 150

<210> SEQ ID NO 268

<211> LENGTH: 124

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 268

ggctcaggtc ctccctacaa gacctaccac tcacccatgc ctatgccact ccatctggac 60

atttaaatgaa actgagagac agaggcttgt ttgctttgcc ctcttttctt ggtcaccccc 120

actc 124

<210> SEQ ID NO 269

<211> LENGTH: 93

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 269

tggagaagca ctggtgtctg cagcacccct cagttoctgt gcctcagccc acaggccact 60

gtgataatgg tctgttttagc acttctgtat tta 93

<210> SEQ ID NO 270

<211> LENGTH: 76

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

ggaggatgcg ctgtgggggt gtttttgcca taagcgaact ttgtgcctgt cctagaagtg 60

aaaattgttc agtcca 76

<210> SEQ ID NO 271

<211> LENGTH: 220

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 271

tctggtagat aaagccctag acctgtgtcca cactctcacc cccatcccca actttccctg 60

gaccgggtgcc gccccactt gatgcttgct caaggccggg gactggagcg ggctacttgt 120

atatttcgtt gtcagtctgc agaatgtgtt tgatttttat ttttccctcc ttctctgaca 180

tgtgtcaagg aataaagact ggatacaggt ccattacgtc 220

<210> SEQ ID NO 272

<211> LENGTH: 98

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 272
tggatcgatg atgagtcctcc ccaaaaaaac attccttgga aaagctgaac aaaatgagtg 60
aaaactcata ccgtcgttct cagcgggaact gaggtcca 98

<210> SEQ ID NO 273
<211> LENGTH: 97
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 273
ggccaaaaag tctacattgc gtgtgtggat ggatgaatga gcagtgggag tgcagcgcca 60
ggtgacaaga tgttgtgagg gggtttgagt catccag 97

<210> SEQ ID NO 274
<211> LENGTH: 87
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 274
gccctgcgcc ggcaaccacc tagtggccca gggaaggccg ataatttaa cagtctccca 60
ccacctaccc caagagatac tggttgt 87

<210> SEQ ID NO 275
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 275
aaaaaagtgc aactagtatg aaagggttat aaagta 36

<210> SEQ ID NO 276
<211> LENGTH: 116
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276
gtgagtaaat aatgttctag tgcaacagga caaactactc tctccacagg aaaccaacc 60
acaacaggat caatagaaag aaaagagaaa acgtagccc ccaactacaa ataaat 116

<210> SEQ ID NO 277
<211> LENGTH: 264
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 277
tttcttcttt atgtccaatt ttgtgggtgg gaggaggatt tagtctcttc ctgatttcga 60
agagctcatt tactatttcg ggaaataaga ttgtgattgt caaccattat agctattttt 120
tacacacttt tcaactttgt tttgtttata agaattgtga tgattgttac atgtccaagt 180
ataaccatgt tcgcttttat ggcttttgag ttcatgtca tttttggaaa gatatatata 240
ttgagtcctat aaaacccttc acct 264

<210> SEQ ID NO 278
<211> LENGTH: 119

-continued

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 278

actttaataa aggttatcca taccaataaa aagtgtacaa cacagcattt tctgttaaatt 60

tattattggt ttccagtgtg aatttggtat tttttctggc atgcgtttat taatttatt 119

<210> SEQ ID NO 279

<211> LENGTH: 279

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 279

gtaggtttgg gagtataacg gtcacccagg gaggggggtga agacggagaa gacttacata 60

gcacggctcag gttagggctg gacagatgag gaagagctag caaagggggc ttgaggagca 120

gtggccacta agacaggagt gtgacatttt agaagccaaa agaagacat gtaattcaag 180

ggagaggat gatttgctgg gtcagatcta aaaataaatc acacgttttt ttaaactgta 240

gtaattaacc actgaaaact tatgagtgat ccaatatta 279

<210> SEQ ID NO 280

<211> LENGTH: 130

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 280

gggacaaggt cccttggtgc tgatggcctg aaggggcctg agctgtgggc agatgcagtt 60

ttctgtgggc ttggggaacc tctcacgttg ctgtgtcctg gtgagcagcc cgaccaataa 120

acctgctttt 130

<210> SEQ ID NO 281

<211> LENGTH: 262

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 281

tttactctt getgtctget cctctcacat catccttgcc tctgtctgtt taatcctct 60

gtccttcatt ttcctttttt gcctctgcat tcagcatttc tacttccaat ctccctctc 120

tgctctttct tatttctctt gatctgcaga cttgtctctg tcccctcctt ctgttcccct 180

cctggatgtg tctttggcca acctttcctt ctctgagact tcgtgttctt gttggtagat 240

gggggctgat acctctgggt ct 262

<210> SEQ ID NO 282

<211> LENGTH: 140

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 282

ttattattat gaaccttcag cctactttct tgagtgcctg aaaagtgtt gtaaatTTTT 60

ttttttttta agaagaaaga aaaaaatggt gtttgacgtt gatggaaatt caaaaatata 120

tatggaactg aaacattaac 140

<210> SEQ ID NO 283

<211> LENGTH: 143

-continued

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 283

cttggtcttt tgaagcttgt gctgaggttt tagcttttct atgttttata tgccgtgtgt	60
ttgaaagaga acctagattc tatagttgta ttattgttgt ttcatacttt aaatttatat	120
ggctgtggaa aaacgaatta aaa	143

<210> SEQ ID NO 284

<211> LENGTH: 151

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 284

gtgtgtcaag gatttgacaa actgccattt ttctccagaa gtcaagcccc taagtgttg	60
tctagaggca agaatttttt gatatgttgt ctcaacaatg cttctcactt cgtcttcagg	120
tgccccaacc cgcaagtaca catactatgt a	151

<210> SEQ ID NO 285

<211> LENGTH: 150

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 285

aatgttcata ggtttctaac cctcaccccc caccacggga gactagagct gcaggatccc	60
aggggagggg tctctctccc caccacaagg catcaagccc ttctccctgc actcaataaa	120
ccctcaataa atattctcat tgtcaatcaa	150

<210> SEQ ID NO 286

<211> LENGTH: 115

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 286

gatgggaatt gagatgtaag atttgggggt gagggtcgtg ccaattacat ttcatttgca	60
tggatttttg ttttcatgct ctgtctctcc ctctcttggt cttactgggt ccctc	115

<210> SEQ ID NO 287

<211> LENGTH: 223

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 287

tacattgtaa gagcaacatc ctacgttaat aaatgttcta gcccggtgct tcgcgaacat	60
ttatgtgcat acaaatcacc tgggatcttg ttagaaggca gtaggtctgg ggtggggcct	120
gagattctgc atttctaacc aggtctctgg agatgctgat gctatcgagc cacaaccaca	180
ctttgagtag caagcctctg gcctatcctt attgtttgtt ata	223

<210> SEQ ID NO 288

<211> LENGTH: 272

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 288

tttactctt gctgtctgct cctctccat catccttgcc tctgtctgtt taatctctct	60
---	----

-continued

```

gtccttcatt ttctttttt gcctctgcat tcagcatttc tacttccaat ctcctctctc 120
tgctctttct tatttctct gatctgcaga ctgtctcttg tccctctctt ctgttccct 180
cctggatgtg tctttggcca accttctctt ctctgagact tcgtgttctt gttggtagat 240
gggggctgat acttctgggt ctgggcatg tc 272

```

```

<210> SEQ ID NO 289
<211> LENGTH: 221
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 289

```

```

ttgctggggc ttgtcctaga ggctccagct ttggcacagt ggttcctggc tgctgccatg 60
tttcagatga ggaggagag aaggaggccg ccagactcga gaggtgggag gaactccttg 120
cacacacct gagcttttgc cacttttata atttttgagc aactcccttt cagctaaaag 180
gccacccctt tatcgcatg ctgtccttg gtagaatata a 221

```

```

<210> SEQ ID NO 290
<211> LENGTH: 183
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 290

```

```

acaaaactct ccaataatga ctctgctcag ctccagggca gcaggagtgg agtgtcgggg 60
gcccttggtg ctgagtgaag ataaattaaa aatcccaaca agccagtgc attatgtaca 120
ggaggaaaagg ggtggggcct ccaggacaga gcccgagggt ggcagggcag gacttgagtg 180
ggc 183

```

```

<210> SEQ ID NO 291
<211> LENGTH: 237
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 291

```

```

cagacacatg agcaggactt tggggagtgt gttttatata tgctcagatgc ctagaacagc 60
acctgaaata tgggactcaa tcattttagt ccccttcttt ctataagtgt gtgtgtgcgg 120
atatgtgtgc tagatgttct tgctgtgtta ggagtgata aacatttgc catgttatat 180
aggtggaaaag ggtcagacta ctaaattgtg aagacatcat ctgtctgcat ttattga 237

```

```

<210> SEQ ID NO 292
<211> LENGTH: 189
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 292

```

```

tcaagttaat ggcagctaaa acgctcccag tccatttatt ggccacatga ggtggtcgtc 60
aagaaacaag ttagaagggt atgacaggaa gtagtataat aaatgcccg cagtacgagg 120
ggttcaacag aagtgaacaa ggcacaagaa agaggtctgt gttcaggaaa caggccagtc 180
cccacatgg 189

```

```

<210> SEQ ID NO 293
<211> LENGTH: 246

```

-continued

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

```
tgaactaaaa ctatgagcct tattcaatat ctataattct atgatttttt taaattatgg      60
gaaattaatg aaagatgttt acatgaataa tgtttgccct tactgtgtta tgaatgagtt      120
ttttgtagtg tgtctgggtg catgatgcaa gagagtagga aaaatgtttt tgaacaaaaa      180
cttgacaaat atttgtaatg aaagtaaatt taaagattgc tataattgcg ctatagaaac      240
aatgca                                          246
```

<210> SEQ ID NO 294

<211> LENGTH: 65

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 294

```
ttaacagtac atttgtgtgg ctctcaaaca tccctttgga agggattgtg tgtactatgt      60
aatat                                          65
```

<210> SEQ ID NO 295

<211> LENGTH: 120

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 295

```
tacaatgatg gttgagtga aatacagaag gggggtttga gtattcagat ttcataaaac      60
acttccttgg aatatagctg cattaacttg gaaagaagcc tggtagggcca gaagacagaa      120
```

<210> SEQ ID NO 296

<211> LENGTH: 156

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 296

```
aaactgatgg aaaggaccaa ttatttatag ttcccaaca aaagttttaa gatTTTTTtac      60
ctttgcatca gtgcattttt atttatatca aaaggtgcta aaatgattca atttgcattt      120
tttgatcctg tagtgcctct atagaagtac ccacag                                          156
```

<210> SEQ ID NO 297

<211> LENGTH: 169

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

```
tgttaaactt tggaacacct accaaaaaat aagtttgata acatttaaaa gatgggCGTT      60
tcccccaatg aaatacacia gtaaacattc caacattgtc ttaggagtg atttgcacct      120
tgcaaaaatg gtctggagt tggtagattg ctgttgatct tttatcaat                      169
```

<210> SEQ ID NO 298

<211> LENGTH: 87

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 298

```
aaatgacttt caactaacct tgtgaatctt ttgcagtgtg ctgtgtgcaa taccaagggc      60
```

-continued

atagctccct gtaatttggg aaataca 87

<210> SEQ ID NO 299

<211> LENGTH: 96

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 299

catatatttt ttgctacttt tgctgtttta tttttttaa ttatgttcta aacctatttt 60

cagtttaggt ccctcaataa aaattgctgc tgcttc 96

<210> SEQ ID NO 300

<211> LENGTH: 269

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

tgctggcact gatattatcc atcatctctt ttgggacact tctgtaaatg tgattggatt 60

gtttgaaaga agatttaaag tttcaaagt tttgttctg ttttgcttt gcatttgag 120

aaaatattga aagcaggga tgtgtttca ttcacctga aaaaaccatg agtaaatggg 180

gatatagaat ctctgaatag ctgcgtaaaa gattcaagca agggacatga attttgttcc 240

atctatcaat aatatccaga agaacaact 269

<210> SEQ ID NO 301

<211> LENGTH: 188

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 301

tctgtgtgtg tcttagcatg gagagtccct tcttttccc ttcagttagg ttgaccttt 60

ccatttgttt agtatccgtg cacatgtcgt actagacccc aatcaagttg cttattttaa 120

attctttcag ctgtttccct attatttcct tactttgctg aacatgtccg ctgttttacc 180

tcaactgct 188

<210> SEQ ID NO 302

<211> LENGTH: 246

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 302

ggagccaaca attcgagtgc aaacatgatg gctcagaccc ttctctgcc tttactagcc 60

ttcatgatct gtcgggtctc agcagctcag gccacaggag gaggtgggtc tctgactgg 120

cctgtgcatt ctcccaaaca agatgtttaa gactcttctt tatctcgtca caaacgcaca 180

ggacacacac gcacacacat gcacacacag ttacaaacg caccgtacac acacgcacga 240

cacatg 246

<210> SEQ ID NO 303

<211> LENGTH: 217

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

agcgaaggga aggttgccggg agaaagagcg ggggccgggg ccagacgcca agaggggcgc 60

-continued

ggggagcaca gagaagcggg ggggaagggcg ccacgtcgag gggccggggg aggcggtgac	120
tggggggcg agtggaggct gcacccggac cgcggggcgcc cagctcggtt tgggcccgcg	180
gagccctctg ccgtcgcgag cccgggcctc gggaggg	217

<210> SEQ ID NO 304
<211> LENGTH: 172
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304

tgcagtgcta gtcccggcat cctgatggct ccgacaggcc tgctccagag cacggctgac	60
catttttgc cgggatctc agtcccggtt cccaagcac actcctagct gctccagtct	120
cagcctgggc agcttcccc tgccttttgc acgtttgcat cccagcatt tc	172

<210> SEQ ID NO 305
<211> LENGTH: 188
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

tattcctggt agaggaatct ctgtatttga aaattctcca gaaggaataa tataaactgt	60
ggactttggg tgataatgat atgtagggtc gtcagttggt aacaaatgta tccctctggt	120
gggggctatt gataatgggg aaggctgtgc atgtgtggga gtaggaggtg tatgggacat	180
ctctgtac	188

<210> SEQ ID NO 306
<211> LENGTH: 242
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306

aaagagtcaa ctttccggcg gcggggggaga aatgataaaa gagagagagg agggcagatc	60
accacctaga agcacatcct ttgttcgcag aggggggaga aaaagtcgga gagaaagaat	120
gaaagagggg aaaaaaggca gttcggcacc cggagaaagg aggcaattcg gggagaggag	180
gaggagaaga agaaaacaca cacgcgcgca cgcacacaca caccgcggag agaaaagaac	240
ag	242

<210> SEQ ID NO 307
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

gtgagcccat atcgtactgc tgcagtcag cct	33
-------------------------------------	----

<210> SEQ ID NO 308
<211> LENGTH: 83
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308

taaccttagg aaaccagaat agcgtttggc agacacgacg ttttcagttt acctttgaca	60
cctgccccac tccattttgc ttt	83

-continued

<210> SEQ ID NO 309

<211> LENGTH: 201

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309

```
c c g g a c a g t g   g c c t t c t c c a   c t c c c c t c t g   a c t t c t c c a a   g g g g g c t c a g   t g g c c a g t g c   60
c c c c c a g g a g   g c t c c a c c c t   c a a c t c a a c c   c a a g c a a c a g   g g a c a g a t g a   a a a a c a a a t   120
c c a a t c a g g g   c g a t a a a t g g   c g g g g g g c a g   g a c g t g g t g g   t c t c c a g g c t   g g e t t c g t g c   180
g t t c t t g c t t   t t g t c a c t g c   c                                     201
```

<210> SEQ ID NO 310

<211> LENGTH: 275

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 310

```
a c a c a a t a c a   a t c a g g a g t t   t t c a a a t t t t   t g a t t c a g t a   t t t g a a t t t c   t t c t t c a t a a   60
a t g t a g t t g g   a a t t t a t c c t   a g t a t t t t t c   t t t a c c t g a a   g g a g g g c c a t   t t a t t t t t a a   120
t t t c a c t a c a   t t t t t c t t t g   c a t g a t t a t t   a a a a t a a a a a   c t g c c t c t g t   t g t g t t t c t c   180
a c t g g a g g c t   g g a a t g a a t g   a t c a c t a g a a   c a c a a a a g a g   t g a a t g a t g a   c a c t t g a a g t   240
c a a a g c a g t t   g t a c t g a t c a   c c a g a a c c a a   t a a a g                                     275
```

<210> SEQ ID NO 311

<211> LENGTH: 220

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311

```
c t a a t t g a t t   a g a a c t g a g t   c t t t t a t a t c   a a g c t a a t a t   c t a g c t t t t a   t a t c a a g c t a   60
a t a t c t t g a c   t t c t c a g c a t   c a t a g a a g g g   g g t a c t g a t t   t c c t a a a g t c   t t t c t t g a a t   120
t t c t a t t a t g   c a a a a t t g c c   c t g a g g c c g g   g t g t g g t g g c   t c a c a c c t g t   a a t c c c a g c a   180
c t t t g g g a g g   c t g a g g t g g g   a a g a t c c c t t   a c t g c c a g g a                                     220
```

<210> SEQ ID NO 312

<211> LENGTH: 187

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 312

```
t t c t t t a t a g   t g t t a t g c t t   a t t t t c a a t t   t t t t t t t t c c   t g a t t c t g t c   t g g t a c t t a g   60
a a t t g t a g t g   t c t t c a t c a t   c a a t t a a a g a   a a a c t g t c t a   a a t g a a t t c a   t g g a t g t a a a   120
t a t t a g t g g t   c c t t a a t g t c   t t t g a t t g c t   g g a c a t g a a a   c a a a c t g c c a   a t t a a a t t t t   180
g c g g a g a                                     187
```

<210> SEQ ID NO 313

<211> LENGTH: 176

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 313

```
t c c t g c a g g c   a t c c g t g g g g   g a a a a a a a a t   c t c t c a g a a c   c c t c a a c t a t   t c t g t t c c a c   60
```

-continued

 acccaatgct gctccacocct cccccagaca cagcccaagt cctcccgagg ctggagcgaa 120

gccttctgca gcaggaactc tggaccocctg ggcctcatca cagcaatatt taacaa 176

<210> SEQ ID NO 314

<211> LENGTH: 266

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 314

aaatgtttga cattcattat cagaatgagg gaaaatttaa acaattccgt tttttctttt 60

gctagtaggc atattatgct aataaaatta ctaaattaaa agtgtgtcaa ggatttgaca 120

aactgccatt tttctccaga agtcaagccc ctaagtgatt gtctagaggc aagaattttt 180

tgatagtgtg tctcaacaat gcttctcact tcgtcttcag gtgcccacac ccgcaagtac 240

acatactatg tactcacttg aaaatg 266

<210> SEQ ID NO 315

<211> LENGTH: 286

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 315

aactgggggc tctgtggggg ctctgtatat agctatgaag aaaacacaaa gtgtataaat 60

ctgagtatat atttcatgt ctttttaaaa gggctgttac cagagattta cccatcgggt 120

aagatgctcc tgggtggctgg gaggcacag ttgctatata ttaaaaacaa aaaagaaaaa 180

aaagaaaaat gtttttaaaa aggtcatata ttttttgeta cttttgctgt tttatttttt 240

taaattatgt tctaaaccta ttttcagttt aggtccctca ataaaa 286

<210> SEQ ID NO 316

<211> LENGTH: 278

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (214)..(214)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 316

gctggtctcg ggcaacaagc agcctcctag gagcagaagg tgatggaggg ccacgggggc 60

agggaggagc agatggccat gtggctcagc cctgctctgg gaaagcgagt ccacagttca 120

ctaacaacaa caataccatc cacaacaaag tagccacaaa gaccacagtt agcaaacaca 180

cacagtcaca cacacacaca cacacacaca catnacggga ggtgggcagg accgcagttc 240

gcagtgggga ggcaagtgtt agttgcatca tcaggtgg 278

<210> SEQ ID NO 317

<211> LENGTH: 122

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

aggtggtgtt ggcagaggct atcggtgttg acaaggacaa acccaaccgt gtgaccaaag 60

tggtgtgtaa gatgttgaag tcggacgcaa cagagaaaga cttgtcagac ctgatctcag 120

aa 122

-continued

<210> SEQ ID NO 318

<211> LENGTH: 161

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 318

aatgaaattg ttaattggcc aggcacagtg ggaagcacct gtagtcccag ctactcagga 60

ggctaaagtg agaggggtggc tctagcacag tcatcaaggc tgcaggaggc tatgatggag 120

ccactgcact ccagcctaga tgacaagggtg agacgctgtc t 161

<210> SEQ ID NO 319

<211> LENGTH: 162

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 319

tgtttttgac atcagctgta atcattcctg tgctgtgttt tttattacc c ttggtaggta 60

ttagacttgc ccttttttaa aaaaagggtt ttgcatcggt gaagcatttg acccagagtg 120

gaacgcgtgg cctatgcagg tggattcctt caggtctttc ct 162

<210> SEQ ID NO 320

<211> LENGTH: 114

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 320

tttttttagtt gccaacagtt tatgtttgct gattatttat gacctgaaat tatatatattt 60

tttttttaag aagacatttt gttacataag gatgactttt ttatacaaag gaaa 114

<210> SEQ ID NO 321

<211> LENGTH: 223

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 321

gcatttgaat tgactaggct ttccctatat aaaaaactca aaacttgta actctgtact 60

ttaataaaat ttaaaattaa aactgtgttg tttttttctc ttctgctaga tacatatata 120

attaaagtac tcaagttagt tggtttgcag agatgttgcc ttcagatggt aatcagggtc 180

ctcaagtttc atggagtcta tgetgatcct ttaattgaca aat 223

<210> SEQ ID NO 322

<211> LENGTH: 289

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 322

tatacagaat agtcactggc cttgggctaa atggtgactt caagtgtagt ggctgcatag 60

tcaaaaaatga attagatgag tacaaaagtg acgaaatgaa agaattgcaa gaatggacca 120

caaagacagt gttttatgac ctaagatta agatttatcc atttgtgtac aattgtggac 180

tatataaaat aaaacaagac ttgacctca gtggataaga agtatttgga tgtactaatc 240

aatatttttg gtctgggtca gtgggtgggt catctgtgtt tgttgatt 289

-continued

```

<210> SEQ ID NO 323
<211> LENGTH: 246
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 323

tccaacaaca gtgctgaactg tccggataag agctggcaag tgcccttagg atgccgcatg      60
ggaaaaatcg gttatcataa tttcaaagta taaatatatt tattatgtag cgctgcgggt      120
aagaaggaag agtgaggggt ctgtccatgg ggtggcagtg atttcccacc cgcctttctt      180
gaatggcttc gtgttattca gccgtgccct ggcaggaatg gaactccatc agggaacagg      240
gcagct                                           246

```

```

<210> SEQ ID NO 324
<211> LENGTH: 156
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 324

aatatacctg atgcgctgta gaatgaaaat gtaaaagata acctgtatgt gttccgagct      60
ttaatttttt gtttacaat tgaacagtgt tacatgggct gtccagtcct gattatagag      120
aggaagaaat ggtaacagta tggcagataa gaatta                                           156

```

```

<210> SEQ ID NO 325
<211> LENGTH: 298
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 325

agcaggagta agtttctcat cccatgggcg accagggcca tctcctccca ccagtggccc      60
ccactcacag ggagctggca atgccctacc tgccctgtct ccagatggag aaacaggctc      120
tgagatttca caggtcttgc ccaaagtcac tgattttgat gattaaaaag aataaacaca      180
gtgtttcctg agtagcagtg attgttatgc cttgctatct taataaagat tctattttcg      240
tataacattg tcaagtggaa acatgctgaa atctattaaa ccatctttgt ttgtggaa      298

```

```

<210> SEQ ID NO 326
<211> LENGTH: 98
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 326

aaagagtcaa ctttccggcg gcgggggaga aatgataaaa gagagagagg agggcagatc      60
accacctaga agcacatcct ttgttcgcag aggggggga                                           98

```

```

<210> SEQ ID NO 327
<211> LENGTH: 103
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327

gtttgtcttg cgcagtgtt actccagctg tggcatgcag gtgtcagcaa gtatgatcag      60
caatgaggcg gtggtcaata tctgtcgag ctcacacca cag                                           103

```

```

<210> SEQ ID NO 328
<211> LENGTH: 191

```

-continued

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 328

```
aatctctttt tttctggagg ctggcacctg attttgtatc cccctgtagc agcattactg    60
aaatacatag gcttatatac aatgcttctt tctgtatat tctcttgtct ggetgcaccc    120
ctttttcccg cccccagatt gataagtaat gaaagtgac tgcagtgagg gtcaaaggag    180
agtcaacata t                                191
```

<210> SEQ ID NO 329

<211> LENGTH: 220

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 329

```
tgcccccagt atgtttagga cgcgagcccc agaaggattt gggagtaaac ttaacattca    60
ctgtgttttt gctttgcatc cgccatttgt gtgtgttttt ggactgtggg ctgtgtgtac    120
cttggttggt gactcagtga gaagaagcag gaatgcaaaa gatactatga atgttttgag    180
ttttgttget gttgttggtg agaggttgtt tcaactggtat                        220
```

<210> SEQ ID NO 330

<211> LENGTH: 258

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 330

```
gatcgtctgg taactttota actttaaata atatgtttga gcaataattt cttgacttac    60
tgactttaca acatctttaa taattcccca ttacaaaaga taaggattta acttacacta    120
tcgccacttt cctttgtoca tctctctcca aatgtctgat agttacatca ctttttaata    180
catctattgg tttgatttta tagctttgaa caatacacta atcctctagt tcttgttcca    240
ttaactgaag atcttttc                                258
```

<210> SEQ ID NO 331

<211> LENGTH: 233

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 331

```
gaaacacaag agacttaaag gacaggagga ggagatggcc ataggagagg agggttcttc    60
ttaggtcaga tggaggttct cagagccaag tcctccctct ctactggagt ggaaggtcta    120
ttggccaaca atcctttctg cccacttccc cttccccaat tactattccc tttgacttca    180
gctgcctgaa acagccatgt ccaagttctt cacctctatc caaagaactt gat          233
```

<210> SEQ ID NO 332

<211> LENGTH: 96

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

```
ggatcgatga tgagtccccc ataaaaacat tccttggaag agctgaacaa aatgagtgag    60
aactcatacc gtcgtttctc tcggaactga ggtcca                                96
```

-continued

```

<210> SEQ ID NO 333
<211> LENGTH: 181
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333
tggtgacaga gtttgggacc gaggtggagc ccgagtttgg gaccaagggtg gagcccgagt      60
ttgagaccca gttggagcct gagtttgaga ccagctgga acccgagttt gaggaagagg      120
aggaggagga gaaagaggag gagatagcca ctggccaggc attccccttc acaacagtag      180
a                                                                                   181

<210> SEQ ID NO 334
<211> LENGTH: 135
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334
gatatcagat cagttgagac taacagttga aagcagtaaa catattacgg acatattatt      60
gataaaagac atttatgaag aggataaact gtgaagggtg acagacacta aaccatagtt      120
gctaaacaca taaaaa                                     135

<210> SEQ ID NO 335
<211> LENGTH: 80
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335
agagccagga cagtgaggtc aactttgaca attccatcca ccagaaagtc ttggagctgc      60
tgcttgacta tgcgtactcc                                     80

<210> SEQ ID NO 336
<211> LENGTH: 96
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 336
ggatcgatga tgagtcccc ataaaaacat tccttggaag agctgaacaa aatgagttag      60
aactcatacc gtcgttctca tcagaactga ggtcca                                     96

<210> SEQ ID NO 337
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 337
ttgacagtct gccttactat gaaattctag gtacaaaaat ttcccttaag ctctgaagat      60
gttgatccat tgacttctgg cattcagtggt tgctgatgac aaatctgtta gcagtctatt      120
tctcatccat ttttgtgttg agctaactgt gatgacctca tttgttttct ccctggccac      180
tttaatatct tccttctatc cttaatatcc caaaatttta caatattgtg tctagatgta      240
gattgtattg ggccctctca atctggagac ttagcttgct ctgttcttca                     290

<210> SEQ ID NO 338
<211> LENGTH: 197
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

-continued

<400> SEQUENCE: 338

atgtcaagaa aatgacgggc acagaccagg tgaactgccc caagetctcg taaccagggt	60
ctacaggagg gctgcaccca ctccatgtta cttctgcttc gctttcccct accccacccc	120
ccccccataa agacaaaacca atcaaccacg acaaaggaag ttgacctgaa catgtaacca	180
tgcctacccc tggtacc	197

<210> SEQ ID NO 339

<211> LENGTH: 113

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 339

tgtcactggg gaaagacgac ttgggtgccc atttttaata aacacaatgc tattagcgtc	60
actccaattt agtgtctgat tgttaaatgt taatgtactg cactctacag ttt	113

<210> SEQ ID NO 340

<211> LENGTH: 183

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

ggattataat atcctcactg gccacaatct gtaaaagtcg atactggcac tttttttgcc	60
ccctcaaagg aaatatgcta atagacagcc cctttgcaaa tataattcct ccttcccaac	120
ccttcaaatt gctaaggccc cactggtcag caccctccct ttcgagtcga ggactactgt	180
tct	183

<210> SEQ ID NO 341

<211> LENGTH: 275

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 341

agcattaata atttccatgc atgtgtcttt ttccagtagg tatgggtgaa tttatgtaaa	60
tttattgcta atcccatccc ttacgattta gagtataagc tgcgcaaggg cagaagtttt	120
tatttggttt gttcatggat gtattttaag agctgagaac agggcctgga cacaataagc	180
attcaataaa tatttactga atgaatgaac tcctacctat attcctattt ataatttggc	240
tccactttat cctacttttag ctccatttca attca	275

<210> SEQ ID NO 342

<211> LENGTH: 123

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

catttaataa agaggagatc cacaaagagc aacagagata agagaagaaa ggaaataatc	60
aataaaataa ttcaagaaaa tccaaggaca tgagttttca gattgtaaga gactacttga	120
gtg	123

<210> SEQ ID NO 343

<211> LENGTH: 99

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 343

aattcatatc cctgttctgt ctcatgcgcg tcctccgtcc ccaatctaaa aagcaattga 60

aaaggtctat gcaataaagg cagtcgcttc attcctctc 99

<210> SEQ ID NO 344

<211> LENGTH: 97

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 344

tggatcgatg atgagtcctc caaaaaaaca ttccttgga aagctgaaca aaatgagtga 60

gaactcatac cgctggtctc atcggaactg aggtcca 97

<210> SEQ ID NO 345

<211> LENGTH: 119

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 345

attttctatc tgtggttgga ttcagaccac atgaacactg agggctgact gtagttttga 60

atgtctgtta ctgaggaggc accagcataa agtatatttat cacttcagac gctgacaat 119

<210> SEQ ID NO 346

<211> LENGTH: 121

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 346

ttatatattat gtttagcacc gtcagtgttc ctatccaatt tcaaaaaagg aaaaaaaga 60

gggaaaaatta caaaaagaga gaaaaaaagt gaatgacgtt tgtttagcca gtaggagaaa 120

a 121

<210> SEQ ID NO 347

<211> LENGTH: 168

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 347

gtttgagcta tcgaagagta agtaaccaga aatttgagaa cagcctgggc agcatagtga 60

gaccccatct ttacaaaaac ttcacagatt agccaggtat ggtggcattt tcctgtagtc 120

ccagctactc agaatgctga gccaggagag tggcttgtag ccaagagt 168

<210> SEQ ID NO 348

<211> LENGTH: 47

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 348

aggataaact tgtgtggtgt agagaagtta aaatcctcac gttgtac 47

<210> SEQ ID NO 349

<211> LENGTH: 286

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 349

-continued

acttcaggga agtttcataa aaggaagaat tttaactcag cgtagaaaga tgggttaaatt	60
ttcctcatgt gaaggtgtac tgccctgggt gctgcaggct ggagatgagt attaaaaatag	120
gaggagagtg agtgaagca caggaggagg aagggtcagg caagtttggt gaacacagca	180
actggctata gaacaggagc agtgggagaa agtccagaaa ggtctgctga gcttcagttg	240
tacaaagctg tggagtttgg cctttggtca tggctagatt aggtct	286

<210> SEQ ID NO 350
 <211> LENGTH: 94
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

tggatcgatg atgacctcaa tacatgcatt ccttggaag ctgaacaaaa tgagtgaana	60
ctctataccg tcgtcctcgt caaactgagg tcca	94

<210> SEQ ID NO 351
 <211> LENGTH: 174
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 351

gtttgaggta tttaactgac acctaaagtg atctgttgag gaaacagttg gatatacaaa	60
tttagtggtt aaggcagact tccaggcttg aaggaaaaat ttggaagtca tcacgacata	120
tatgtggtat ttaaaattgt gaggttcaag gaccaagccc cataccattt agag	174

<210> SEQ ID NO 352
 <211> LENGTH: 255
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

tggagatagc tcttaaagat ataaatgttt atggctgaaa tggtatggca tcttgattt	60
gctttaaaat aaccagctt gctgcaggag gtgggtattg tgtgtgtggg aagggtggga	120
ggctgcggga ggaagagatg acccaagatt aggcagatgt tggttaactgt ggaagcaggg	180
tggtgagtg gggctcatga cattatgctc tctactttgt gtacgtgtga acatttcctg	240
aataaaagat gcctt	255

<210> SEQ ID NO 353
 <211> LENGTH: 137
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 353

ggattttttc cctgtagta gtgaggtaac atgcttgaat gtcactgtga tatttatttc	60
ctctttgttc agttgttttt gaattcctgt taagtacatg ttttaatact ttgagcgatt	120
taagatactt ttctttt	137

<210> SEQ ID NO 354
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 354

-continued

aaacgatgat aatctttact ggtgaaaagg atg 33

<210> SEQ ID NO 355
 <211> LENGTH: 195
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

tatgagttat tcaaggagga gactttttaa agacagcaac gcaattcttg taacttgtgt	60
aaatagcccc atctttcaga gtgataccat ttctacattt gataatgcct gtattcctgt	120
aggatgtata tagtttaggg gatttttttt ttgtttggtt ttgttttta gaagtcaata	180
tgtctggttt tattt	195

<210> SEQ ID NO 356
 <211> LENGTH: 255
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 356

attattttga tagcagatgt gctatttatt tatttaatat gtataaggag cctaaacaat	60
agaaagctgt agagattggg ttctattgtt aattgggttg ggagcctct atgtgtgact	120
tatgacttct ctgtgttctg tgtatttgtt tgaattaatg acctgggata taaagctatg	180
ctagctttca aacaggagat gcctttcaga aatttgtata ttttgagtt gccagaccaa	240
taaaatacct ggttg	255

<210> SEQ ID NO 357
 <211> LENGTH: 217
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

gtgtgttaaa atgagggctc cactgcttta ggattgaagt ggctggaaag agtgcgcct	60
ggggaaggag atggagttat gagggactg tggtgggtac tttctgtact aaacatttcc	120
tttttctatt ttaccactaa ttttgttta aactgtgagc cgtccaagtc agaagaagac	180
agcaaaaaaa gcaacttttc caacatacaa tttactt	217

<210> SEQ ID NO 358
 <211> LENGTH: 92
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 358

cctgcctggg aaagcgagtc cacagttcac taacaaacac aataccatcc acaacaagt	60
agccacaaag accacagtta gcaaacacac ac	92

<210> SEQ ID NO 359
 <211> LENGTH: 251
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

atataattgg acaaacgctg gcaaaaagaa aaaaatggta agcaaaaaac ccaagataaa	60
gtttcgagga catcaggcct ttgaaatac aatgtcaaat gacacattgt acggtttcaa	120

-continued

aaaatccgct agacatgtca taagttttaa ctgtaatgcc caggaaagga tatcttaaaa 180
tattctaaac ttgtgtaaca aaggaataat taactgtaat agtttttcaa taaatcgagt 240
tggtgtgttc c 251

<210> SEQ ID NO 360
<211> LENGTH: 261
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 360

gaatgggttac tgtttatact gtggtatgtt ttgattaca gcagataatg ctttcttttc 60
cagtcgtctt tgagaataaa ggaaaaaaaa tcttcagatg caatgggttt gtgtagcatc 120
ttgtctatca tgttttgtaa atactggaga agctttgacc aatttgactt agagatggaa 180
tgtaactttg cttacaaaaa ttgctattaa actcctgctt aaggtgttct aattttctgt 240
gagcacacta aaagcgaaaa a 261

<210> SEQ ID NO 361
<211> LENGTH: 175
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 361

tatttcttgc tatttgata tgacaagaga cttaacttat cttgctctgt tttccctgt 60
acacgctgta tataggggtc aatgtgatgc tgctggagac gagaataaac tggactagaa 120
tagtgcattg tatttagtct gtattgatca tggatgcct ccttaatagc catat 175

<210> SEQ ID NO 362
<211> LENGTH: 251
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

gaaccgcaga ttatggttaa tccaattctg tgcacctgag gtccataaat aaaagaataa 60
gtattgaaat gaaagaatga cagaaagaat gaatggacac atgaacgact gaattagaaa 120
tggaatgcc tggcacagcc aggaaggagc tgcccatggg attgtcattc atttcaactc 180
gggcacctga ggtccataag cgtgaaaaga ggcaggaaga gaagtgtcag ggagtcaaag 240
atagagctaa g 251

<210> SEQ ID NO 363
<211> LENGTH: 237
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 363

ttattttatt tcgctatttc cagtttgaag ctactatcat gggcgtttag agttatacaa 60
atgacactta caaaaaataa aagaccaaga caccagagt gagatgcatg ttggggacgg 120
gggaggctgg cagcaggggg gccccggcgg ctcaccccag ggctcccga gggggctgtt 180
tccatccacc acccaaaaaa acaccacaag ggtcagtcct agcccacccg acagctt 237

<210> SEQ ID NO 364
<211> LENGTH: 133

-continued

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

```
gtatggatgg gtatgttgag actcaattac ttttttatta gcttccccgt ttggaagatc    60
ccaaacacca aagatggaag gtgaaaataa agactgcgtg accgggaaga aagtttgaat    120
tactaatagt ggg                                           133
```

<210> SEQ ID NO 365

<211> LENGTH: 263

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 365

```
aatcaaccaa tgcaaccagt ttgtgagaaa aaaaaaaaaa agccgaaaaa aaaaaaaaaa    60
aacacctgaa tgcggaagag ctcggtctcc gtttagcatt ttgtacttaa ggaaataaaa    120
aaccaacaaa ggatttcaca tttttttaa aagtgaagat tgctgtatac tatttattca    180
acttataatt tatgttactc cttgatcttt gtcttttgtc atgacaaagc atttatttaa    240
taaagttatg cattcagcaa ctt                                           263
```

<210> SEQ ID NO 366

<211> LENGTH: 48

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

```
taggttgtca acaggtacta ttgtcacat aactaacttt cgaggcac    48
```

<210> SEQ ID NO 367

<211> LENGTH: 161

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 367

```
attagtgaac ttatctttgc agctgagtac ttaaattctt tttaaaaga taccctttgg    60
attgatcaca ttgtttgacc cagtatgttt tgtagacacg ttagttataa tcaccttgta    120
tctctaaata tgggtgtgata tgaaccagtc cattcacatt g                                           161
```

<210> SEQ ID NO 368

<211> LENGTH: 286

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 368

```
gtcttcacca actaagaaag ctctgttatt ctggcctggg tgcttgctcc agactcagga    60
acatctggtc aacacaagca tcaactgggt ggggaattgt gtgtgtgctg catcatctcc    120
gactctcttg tagttccttc cttccctccc tcaactctac atgcagacac agacagacac    180
agtctggttg ggacatgcag tggcagctcc tgggtgtataa catctttcac acaccttgag    240
tctatctgct tgctgccttt gactgaccc gaaatgggtg gccttt                                           286
```

<210> SEQ ID NO 369

<211> LENGTH: 208

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 369

```
gaggccccag aggacttata tcagctgtac atgctctgcc tgtggagaca tggtttttct    60
ttgtgctgtg gcagactggg gctttggaag tgggtgtatgt ttaacttacc tgagagttag    120
agatgtgtag gaagaatagc tggaagaaag tgaaagatga gtgccagtac ttttgacctg    180
ttatccagta gagagaaaagt gacagtga                                     208
```

<210> SEQ ID NO 370

<211> LENGTH: 201

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 370

```
aactctgtaa ggaggacctat gtcagactat tgtaagctaa gcattaggac tgatacaaat    60
aatatatgct cctggcatag aaaaataaac cacagagaac gagttcaaag aatagcaaag    120
aaagaaagag gaccagtggt gcgaaagatg agagtgtact tttacaaaaa gttatctaag    180
cctgagcact tgaagtctgc a                                           201
```

<210> SEQ ID NO 371

<211> LENGTH: 119

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (91)..(91)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 371

```
aaaatagaga gacataacctg gctccaaaac aaggctgtat cttctgccac tgtaataaaa    60
tagatgcaat tgagggtcat aaataaaaga ntaaatactt aaacgtgaaa ggtgactaa    119
```

<210> SEQ ID NO 372

<211> LENGTH: 36

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 372

```
ataatgaaag ttagtaacgt ccattattta ataaag                                36
```

<210> SEQ ID NO 373

<211> LENGTH: 91

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 373

```
tgtacagggt cattttgaca gtaactggta tattcctttg cattttatgt tgcattgccca    60
atttttagtg tatccagttt gaaagtataa t                                           91
```

<210> SEQ ID NO 374

<211> LENGTH: 178

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 374

```
tactgatctt tatattacag attttttttt cttttaggat tagttcagct tgccccccct    60
ttccatttcc accatttata gtgagcctct ccataattag tgccaacct tagtttcggt    120
```

-continued

catatttttta caccaggagt caacaaactg tggccattgg ccaaatatgg cctcccaa 178

<210> SEQ ID NO 375

<211> LENGTH: 242

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 375

aggaagtacc cgctccataa gacccttaca ttgggacagt caaggtgcac aattgtatgt 60

gaccacaacc atgcaccttg gacataaatg tgtgtaactg cacatggccc atcccatctg 120

aataaggtcc tactctcaga ccccttttgc agtacagtag gtgtgctgat aaccaaggcc 180

cctcttccctg gcctgttaac gtatgtgatt atatttgtct gggttccagt gtataagaca 240

tg 242

<210> SEQ ID NO 376

<211> LENGTH: 199

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

gggagtcaat gaatagtacc taaaatggaa accaaacaaa acaacttcag gaagtaacaa 60

gggcttgctt agagacatga cggtaaaccc tgaaccatca gctaaaagag gtagatagca 120

gtggttgccc ctggggagag gtaaatgtga tggagagggg acaactgtgt acaaacatgt 180

gactttacgt tttgatcaa 199

<210> SEQ ID NO 377

<211> LENGTH: 127

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377

aagagttaaa cagtctagag tgaagggaat gttttaaaat ccagaggcga tcaagtgaag 60

ccaacctttg gaggccgcta gaagtcattt ggaggaattt ggacttcgtg cagtaggaaa 120

gagggaa 127

<210> SEQ ID NO 378

<211> LENGTH: 46

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378

gacagggggtt ctaattactg tctgtgagag ttactacttt gtaact 46

<210> SEQ ID NO 379

<211> LENGTH: 115

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379

taatattttt tgctgcctag gcaaatggct tttgtgaaaa cacttgatg aaaagcaata 60

caccatttgt ttttacttac caatcactat cattaggttt tgatgcaaat gggaa 115

<210> SEQ ID NO 380

<211> LENGTH: 138

<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 380	
ttcccaagcc catgagtcct tgaaaaatatt ttttatatat acagtaactt tatgtgtaaa	60
tacataagcg gcgtaagttt aaaggatggt ggtgttcac gtgttttatt cctgtatgtt	120
gtccaattgt tgacagtt	138
<210> SEQ ID NO 381	
<211> LENGTH: 269	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 381	
cttaggatat gaaatcttca gaggatggta gaagagaaa gtaaatgcc taagaaagta	60
gagtacttgt ggtcattgaa accatggaat ttactcaggg atagtgtata tagtgagaaa	120
tcaggtaact aagatttgag cctaaacgta atctgtaaaa ggggagctca aaggaaaagg	180
gaatgggagg accggatttt gtaaggatag tagggcaaat gttaagagag agaatgagag	240
agttgagtat ggcaaaagt gactcaatt	269
<210> SEQ ID NO 382	
<211> LENGTH: 282	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 382	
tcacctcctg ctggctaccg gggcaggcat gcacccgggt ccagcccccgc tctgggcacc	60
acctgccttc cagccctcc aggaaccggg cccctctgct ccctcactt caggaggggc	120
ctggagcagg gtgaggctgg actttgggg gctgtgagg aaatatactg ggggtcccccag	180
attttgtttt aagggggcca gacctttgc caggctggat tgtacgggccc ccaccttcgc	240
tgtgttcttg ctgcaaagtc tggtaataa atcactgcac tg	282
<210> SEQ ID NO 383	
<211> LENGTH: 131	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 383	
atacctgtta aatagatcaa ttttgattgc ctactatgtg aactcactgt taaaggcact	60
gaaaatttat catatttcatt ttagccacag ccaaaaaataa cgcaatacct atgttagcat	120
tttgtgaact c	131
<210> SEQ ID NO 384	
<211> LENGTH: 183	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 384	
tcacctgagg cgttcaaaag atataaccaa ataacaagt catccacaat caaaatacaa	60
cattcaatac ttccagggtg gtcagacttg ggatgggacg ctgatataat agggtagaaa	120
gaagtaacac gaagaagtgg tggaaatgta aaatccaagt catatggcag tgatcaatta	180
tta	183

-continued

<210> SEQ ID NO 385
<211> LENGTH: 263
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

```
ttgttgtag agacggtgat tcactatgtt ggccaggcta gtcacgaact cctgacctcg      60
tgatccgccc acctcggcct cccaaagtgc tgggattaca ggtgtgagcc accgtgcccc      120
gcctcttttt atttattcct aaaatattac cttgaggcca aattctgcgc ttaaggagaa      180
tgtgcaccaa gtgctgggggt gggggctggt tataaacgag gccacaaatc atgcttgtaa      240
ataaattgtg tggttcaaat ctg                                             263
```

<210> SEQ ID NO 386
<211> LENGTH: 140
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (71)..(71)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (82)..(82)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (94)..(94)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 386

```
cacagccaaa acctctacat ccctacattc acacacttcc tccacacacc atcctgaagt      60
caccccaact nctaccacca anatcaccac caanccacc agtataggaa gcagcacacc      120
catggcccac actacctcag                                             140
```

<210> SEQ ID NO 387
<211> LENGTH: 134
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

```
cagaggagct ttattagagg gacagggtga aacatattta caccggccga gcagggacct      60
taagaagcag gcgtgggagc aggggtccag ctcagacgag ttccaccttg gcattggggg      120
acaccgccac cacg                                             134
```

<210> SEQ ID NO 388
<211> LENGTH: 207
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

```
gagtatgagt atgcctgagt gtgaatgtgt atgagtgtga atgagtgtgt gcacatgagt      60
gcacgggtgt cagcatgtgt atataagtgt gggcatgtgt atgtgattgt gtgagtgtgg      120
gcaggtgagt gtgttgggga tgtgggtag ggtggggagt ggtgctttct ctagtgtgtc      180
ctccggaaca tcttgctac ctacgaa                                             207
```

-continued

<210> SEQ ID NO 389
<211> LENGTH: 113
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 389

gaaaactggt agatgcacac tgttgatttt catggtggat tcaagaactc cctagtgagg 60
agctgaactt gctcaatcta aggctgattg tcgtgttcct ctttaaattg ttt 113

<210> SEQ ID NO 390
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 390

gtttttatta aaacacaaac gcacacacac acaaaattag ccaggcatgg tggccatcc 60
ctgtaa 66

<210> SEQ ID NO 391
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 391

gtcacccag agtcattgtc acctcagagt cattgtcact ccagagtcac tgccacctca 60
gagtca 66

<210> SEQ ID NO 392
<211> LENGTH: 128
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 392

caggctgggc cgtgagcagg tgggccgttg agttacctct gtgtggatc ccgtgcccc 60
acttgccctac cctctgtcct gccttggtat tgtaagtgcc ttcaatactt tgcattttgg 120
gataataa 128

<210> SEQ ID NO 393
<211> LENGTH: 49
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 393

tgattactag tgtaactgg ttattgagat agattatgac attggtgga 49

<210> SEQ ID NO 394
<211> LENGTH: 209
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

cagagtcatt cattgtcacc ccagagtcac tgccaccga gtcattgtca gctcagagtc 60
attgtcacc cagagtcatt gtcacccag agtcattgtc acccattgt caccacagag 120
tcattgtcac ctcagagtcac ttgtcactcc agagtcattg tcacctcaga gtcattgtca 180
ccccagagtc atcgtcacc cagagacat 209

-continued

<210> SEQ ID NO 395

<211> LENGTH: 237

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

aataaatgcc tcaggcgtgc tttttgattc atttgataaa caaagcatct tttatgtgga 60

atataccatt ttgggtcctg aggataagag agatgagggc attagatcac tgacagctga 120

agatagaaga acatcttttg tttgattgtt taaataatat ttcaatgcct attctttgca 180

aggtactatg tttcgtaaat taaataggtc tggcccagaa gacccactca attgcct 237

<210> SEQ ID NO 396

<211> LENGTH: 62

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

tatgtaatta taagatgaag cgtagtgaat tgtacagctg ttgtaataat gacctatttc 60

ta 62

<210> SEQ ID NO 397

<211> LENGTH: 277

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

taccctcttt tatactaat gtagaaaaag cgaaattgaa tctggaaagc aaactgttgt 60

atatagttgc ggtaacaatc atgaagagag agccgggctg tccctcagc aattcatttt 120

aaataacaaa ttatttaaaa ataaaattca tgccagagcc agctgaagag gccttccttc 180

atcaccactg aggccacccc caatctgggc cctctgtcca tctggcatgt ctctcccccag 240

caagattcat ctgttcaatg ccatttgcgt ttcaata 277

<210> SEQ ID NO 398

<211> LENGTH: 203

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

ttttcccaac tctatagcta gattttaaag tcccagtaaa attttgtaa caaaatcata 60

taagaaaagg caaggctggc tcttcctat ggtcctttag tggagctata ttgcataga 120

tcctagacaa atgatgcaaa acaaatccc tccaatttcc actagcaatc tccctaattc 180

gctcaaccct tacataagca tca 203

<210> SEQ ID NO 399

<211> LENGTH: 75

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 399

agaacctgag tataaattta ctttctcaaa ttcttgccat gagaggttga tgagttaatt 60

aaaggagaag attcc 75

<210> SEQ ID NO 400

<211> LENGTH: 248

-continued

```

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 400

aaaaactcaa cctatctggt gttttatttt aatggataaa aatgtaattt ttttaaggta      60
gcaacttatt tccaaattaa tatagatgaa aaatagatac caattagact aaattgaaag      120
ctttttgttc tatatttgca tagcctttga aatatttctt agtgectagg aggtctgggg      180
attcctcttt cgtgggtggtc actaacctta ctgtatgcag ataaaatcac ttgtcaatgc      240
aaaatgtg                                         248

<210> SEQ ID NO 401
<211> LENGTH: 174
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (78)..(78)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (96)..(96)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (123)..(123)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 401

acgagccctc tcacagtgga atggagngca cggctctgaat ctgcacagag caagatgctg      60
agtggagtgc ggggcttngt gctgggcctg ctcttncctg gggccgggct gtccatctac      120
ttnaggaatc agaaaggaca ctctggactt cagccaacag gattcctgaa ctga          174

<210> SEQ ID NO 402
<211> LENGTH: 251
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402

agagagtgga catttgtcgg gaaactccta acatatgccc ccattctgga gagaacacag      60
agtacgacac aatccctcac actaatagaa caatcctaaa ggaagatcca gcaaatacgg      120
tttactccac tgtggaaata ccgaaaaaga tggaaaatcc cactcactg ctcacgatgc      180
cagacacacc aaggtatatt gcctatgaga atgttatcta gacagcagtg cactgcccct      240
aagtctctgc t                                         251

<210> SEQ ID NO 403
<211> LENGTH: 88
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 403

gccctcatgg ttggcatcac atatgcctgc atgccattaa caccagctgg ccetaccct      60
ataatgatcc tgtgtcctaa attaatat                                         88

```

-continued

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<210> SEQ ID NO 404
<211> LENGTH: 284
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404

aactgaaatg tcaacctgtg gactgtggca ttcctgaatc cattgagaat ggtaaagttg      60
aagaccacaga gagcactttg tttggttctg tcatccgcta cacttgtagag gagccatatt      120
actacatgga aaatggagga ggtggggagt atcactgtgc tggtaacggg agctgggtga      180
atgaggtgct gggcccgagg ctgccgaaat gtgttcagct ctgtggagtc cccagagaac      240
cctttgaaga aaaacagagg ataattggag gatccgatgc agat                          284

```

```

<210> SEQ ID NO 405
<211> LENGTH: 214
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405

gacttattec cgctgactga gtttttgagg ggctaccagg aaagcgcctc caaccctagc      60
aaaagtgcag gatggggagt gagaggctgg gaatggaggg gcagagccag gaagatcccc      120
cagaaaagaa agctacagaa gaaactgggg ctccctccagg gtggcagcaa caataaatag      180
acacgcacgg cagccacagc ttgggtgtgt gttc                                  214

```

```

<210> SEQ ID NO 406
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406

gaatggcagt accagaaggc attggttaag tgtcccagga accacacaag cagtgactcc      60
taaagaagtt ca                                                            72

```

```

<210> SEQ ID NO 407
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 407

gcttccttaa aggtcagaac atcaggccaa agtacaacgt ttaatttcag aacttgccct      60
ccaatttaag cattttcaat ttgctctccc catttggtga gtcagaagaa gcagcattgc      120
ccagaaacag gtattacgta acatgcacat actttaaaaa gtactcatcc cttgttttct      180

```

```

<210> SEQ ID NO 408
<211> LENGTH: 173
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408

gttgagtatg ttaagctctt tatgactggt tttgtagtgg tatagagtac tgcagaatac      60
agtaagctgc tttattgtag catttcttga tggtgcttag tcacttattt cataaacaac      120
ttaatgtttt gaataatttc ttactaaaca ttttggtatt gggcaagtga ttg                          173

```

```

<210> SEQ ID NO 409
<211> LENGTH: 243

```

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409

aaaacttggc actttttcgt gtggatcttg ccacatttct gatcagaggt gtacactaac 60
atttcccccg agctcttggc ctttgcattt atttatacag tgcttgcgc ggcgcccacc 120
acccccctcaa gccccagcag ccctcaacag gcccaggag ggaagtgtga gcgccttggc 180
atgacttaaa attggaatg tcatctaacc attaagtcac gtgtgaacac ataaggacgt 240
gtg 243

<210> SEQ ID NO 410
<211> LENGTH: 201
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 410

ccctgctgcc tctgatcgta ggaattgagg agtgccccgc cttgtggctg agaactggac 60
agtggcaggg gctggagatg ggtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgcgcg 120
cgcgccagtg caagaccgag attgaggga agcatgtctg ctgggtgtga ccatgtttcc 180
tctcaataaa gttccccctgt g 201

<210> SEQ ID NO 411
<211> LENGTH: 174
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 411

tgggcgtccg ggcccccaat attcacgcac tcgcaccacg cactcatatt ccctcacc 60
accatcacgg ccccaaagaa ggtcttcct ctgcgaagt ccaccatc ggggtgactg 120
atgttggaag tacacctct cgcctccg gagctgcacc aggcgcgga accc 174

<210> SEQ ID NO 412
<211> LENGTH: 259
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 412

ctacaacagg caggtactgc tgccaggggg ctttgaacta gtgcctgcta ccagagacac 60
ccgggccatg cccctggctg ggcagcctgg cacaagtga gaagaaggca gtgggaaaac 120
tgggtttatt tcaaggcagc agcctgagcc caggagcaga ggaccagtt gttataaggc 180
gctgggagag gatgggcagc tccactgcc ccagagcgga gctcgaagca ccaggttgc 240
ccacggaaaa tccaataaa 259

<210> SEQ ID NO 413
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 413

tttctggggt ctttgagctc caaaaaataa acacttcctt tgaggagag cccccccca 60

<210> SEQ ID NO 414
<211> LENGTH: 159

-continued

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 414

```
gagcttcctt cttcggtctt ggcaccatct tatgaaaagg gtccagatta agatttttga    60
ctgagtcatt ctaaagtaag ttgcaagacc catgatacta gaccactaaa tacttcatca    120
cacacctcct aagaataaga accaacatta tcacaccaa                            159
```

<210> SEQ ID NO 415

<211> LENGTH: 278

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 415

```
ggaagccatt atcctaaatg aactcactca gaaacagaaa accaaatacc acatgttctc    60
acttataagt agaagctaaa cattgagtag acatggatag aaagaaggga accgcagaca    120
ctggggccta cctgaggtcg gagcatggaa ggagggtgag gatcaaaaaa ctacctatct    180
ggtactatgc tttttatctg gatgatgaaa taatctgtac aacaaacctt ggtgacatgc    240
aatttaccta tatagcaagc ctacacatgt gcccctga                            278
```

<210> SEQ ID NO 416

<211> LENGTH: 241

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 416

```
ttcccatctc gtccatgagc ctaggctctg gagccttggt ttggaggctg ctgtgatgtc    60
aggaacgggg atctttctag cttttggcca cttcctggga cctcacgccc ctgttgacag    120
atggagattg ggcagcgggg ccttgctgca ttgttatctg ctgttccgac ttggtttgtc    180
ttgtccaagg gtgacgaaag agccaggcac cagggtctca tgggatgagg tccaactttt    240
t                                                                    241
```

<210> SEQ ID NO 417

<211> LENGTH: 283

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 417

```
gtgagaggta acactctaaa tagcccatth catgctcaag acatccaagt caaagaaacc    60
caatagcaca ggtgagtccc ctctgttccc cccaacacc cactcacat cagggcccct    120
gccctggagt gtcaccttta ttagctgtga gagacacccc agagccctgg gcactgtcag    180
tgattggggg agaacaaaaa caggacctgg tcagagccca cagatgtggc tagaggaact    240
gtgggggtgt gagctccctc ataggctcct gaccacaata tcc                            283
```

<210> SEQ ID NO 418

<211> LENGTH: 186

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 418

```
gagacttgta tgaagatgg ctgtgcctct gcctgtctcc cccaccgggc tgggagctct    60
gcagagcagg aaacatgact cgtatatgtc tcaggctcct gcagggccaa gcacctagcc    120
```

-continued

tcgctcttgg caggtactca gccaatgaat gctgtatatg ttgggtgcaa agttccctac	180
---	-----

ttcctg	186
--------	-----

<210> SEQ ID NO 419

<211> LENGTH: 267

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 419

gcatttcaaa gtgacttota tgaagctttt tttttaatgt gaaattttca gaattgtgtt	60
---	----

tttttcatgt agatactcca ggaagagtta agcactgctt tcagttttta tateccactt	120
---	-----

gaggggtcgc tgcttgaggg ctcttatccc aggggacttt ttaattcgga tgttacttaa	180
---	-----

tgtggcttct ctaatgtagt ttctttgatt accgactaca caattatgta ccatcacagt	240
---	-----

attagtggaa aagtaccatg tgattta	267
-------------------------------	-----

<210> SEQ ID NO 420

<211> LENGTH: 45

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 420

tgcttataca cttacacttt atgcacaaaa tgtagggta taata	45
--	----

<210> SEQ ID NO 421

<211> LENGTH: 241

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 421

aactggaccc tgctgttctc catcttctca gtcagttgtt tcaagtgttc ctgataactc	60
---	----

ctctccttct gttccatcat ctgctcattc tttctttgca tttcctgcaa catttttgc	120
--	-----

gaagcctgtg cagactcagc tttcacaagt tccacttcaa tctccttttc tttttctgtg	180
---	-----

agagtctggt ctgtctggag aattgcatca gtcataagact ccttggaatt caagtatgtc	240
--	-----

t	241
---	-----

<210> SEQ ID NO 422

<211> LENGTH: 159

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 422

gagcttcctt ctctgttctt ggcaccatct tatgaaaagg gtccagatta agatttttga	60
---	----

ctgagtcatt ctaaagtaag ttgcaagacc catgatacta gaccactaaa tacttcatca	120
---	-----

cacacctcct aagaataaga accaacatta tcacaccaa	159
--	-----

<210> SEQ ID NO 423

<211> LENGTH: 107

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 423

tactcccag gctctgtaca ttgctgccac atactcctgc cagcttgggg gagtgttctt	60
--	----

tcacctcacc agtatttatt atcctgcacc acctcactgt tccccat	107
---	-----

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<210> SEQ ID NO 424

<211> LENGTH: 273

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 424

```
tagaagatga cctcggtccg gagctgggta ttcaaattt gctttcatcc agccactgcc      60
caaagccatt ttcttgcccta ctggatgctt acagtgactg tggatacggg ggttcccttt      120
ccccattcag tgacatgtcc tctttgcttg gtgtaaacca ttcttgggag gacacttttg      180
ccaatgaact ctttccccag ctgattagtg tctaaggaat gatccaatac tgttgccctt      240
ttccttgact attacactgc ctggaggata gca                                     273
```

<210> SEQ ID NO 425

<211> LENGTH: 228

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 425

```
atgtaggaga acgtgcccta ttcacacttt gggaagacgc taatttgtga cttttttttt      60
tcaagcctgc catcaaggac attttttaag acccaactgg catgagttgg ggtaatttcc      120
tattattttc attttggaaca acttttttaa cttatatctt ttatagagga ttccccaaaa      180
tgtgtccttc atttttgggc tctcatgttc caaacctcat tgaataaa                    228
```

<210> SEQ ID NO 426

<211> LENGTH: 286

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 426

```
gctgtgttgg ccctcacttg ggattctcag cagttacatg aaagttgtgc tgataatctc      60
ttctcttgta ccaatttttag tcaggcagaa aatggtaaac atgaggggtgc tcttgtgact      120
taatttttgt tcaagggact aaattgctta tgtttatccc ctgtcagcgg agtgggagaat      180
gtcattcatc aataaaccac agccaatagc tggagaattg agatctggtt gaaagtgggt      240
tatggtttac atgctgtact atcctgagga attgcgagat attgct                    286
```

<210> SEQ ID NO 427

<211> LENGTH: 266

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (214)..(214)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 427

```
ccctgcgcct atcaggtcgt gagtccaggg gtctacaagt cccgggcccc ccagttcacg      60
attctggcgc ggacttcgct cccccaagac aacactcgga agccagggcc cgcggcctac      120
aacgtggatc agcaccggaa gccccgcggc tggagtttct ggatccggca ctcggtactac      180
ctggccccgc tggtgaccga cgcggaacaac tganccgcca ggccgggagcg gccccacacg      240
tgtttgctta aagctcgoga gtccgc                                     266
```

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```

<210> SEQ ID NO 428
<211> LENGTH: 270
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 428

ccagggtga gagacacgtg aaggaagatg atgggaggaa aagcccagga gaagtccac      60
cagggaccag cccagcctgc atacttgcca ctggccacc aggactcctt gttctgctct      120
ggcaagagac tactctgcct gaacactgct tctcctggac cctggaagca gggactggtt      180
gagggagtgg ggaggtggta agaacacctg acaacttctg aatattggac attttaaaca      240
cttacaataa aatccaagac tgtcatattt                                     270

<210> SEQ ID NO 429
<211> LENGTH: 227
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 429

gaagatgaag ccccatgctc agtccctccc catccccac gcagctccac cccagtccca      60
agccaccagc tgtttgctcc tggtagggagg tggcctctc agccctcctt ttctgacctt      120
taacctcact ctcacctgac accgtgcacc aacctctcac ccctcctgga aagcaggcct      180
gatggcttcc cactggcctc caccacctga ccagagtgtt ctcttca                                     227

<210> SEQ ID NO 430
<211> LENGTH: 279
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 430

gcatttgctg tgtttcgtta gcactctggc ccaggacaga ccttcaactt ccaaattgga      60
tactgctgcc aagaagttgc tctgaagtca gtttctatca ttttgctctt tgattcaaag      120
cactgtttct ctcactgggc ctccaacctg gttccctttt ttttagcacc acaaataatc      180
aaaacccaac atgactgttt gttttccttt aaaaatatgc accaaatcat ctctcatcac      240
ttttctttga gggttttagt agacagtagg agttaataa                                     279

<210> SEQ ID NO 431
<211> LENGTH: 123
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (52)..(52)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 431

gcggaactcg agactttaag caaacacgtg tggggccgct cccgectggg tngcagttgt      60
ccgcgtcggc caccagcggg gccaggtagt ccgagtgccg gatcccgaaa ctccagccgc      120
ggg                                                                                                     123

<210> SEQ ID NO 432
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 432

```

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gtgctcagta gtcagactgg atagtcogtt tttgcttata cgttagcogt ggggatttag 60

caggaagctg tgagagcagt tt 82

<210> SEQ ID NO 433

<211> LENGTH: 151

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 433

acacagaaga gtgacatggt tacaaacctc aagccagcct tgcctctggc tggggcctgt 60

tgaagatgct tgtattttac ttttccattg taattgctat cgccatcaca gctgaacttg 120

ttgagatccc cgtgttactg cctatcagca t 151

<210> SEQ ID NO 434

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 434

tttaaaatac tcagaggaca ggatcactgt ggaatcgaat cagaagtggg ggctggaatt 60

ccacgcaccg atcagtactg gg 82

<210> SEQ ID NO 435

<211> LENGTH: 109

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 435

aagagaagac tcacagtata aggtctactg aaggagatac ggtgattcct gttcttggct 60

ttgtagattc atctggtata aacagcactc ctgagttatg accttttga 109

<210> SEQ ID NO 436

<211> LENGTH: 118

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 436

tttgaagatt agaaatttag ccgtaggtaa agaatacaaa ggaaaaataa ttttaaaatc 60

atcaaccaga tcaacaaaat atatgttaat gccgagactt tgaattagag tgcgaatt 118

<210> SEQ ID NO 437

<211> LENGTH: 242

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 437

catcttctag cagatctttt tcagttaaga ttacttggtc ttccatgtat tcatatttag 60

ccagctcctt gatcagccgc agtatgtcac tgcagtcggc ggcagtggct gggcggatca 120

cgaatttagc cattttcgtc ttttgtttt cttccctttg cggaccaggc ccctgtactt 180

gaacagtagg aggaggtggg tcttcattcg tctcccgga gcgtcctctt ctcagtcagg 240

ct 242

<210> SEQ ID NO 438

<211> LENGTH: 34

-continued

```

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 438

gaaatcattg tgggattgct agctttccct ctta          34

<210> SEQ ID NO 439
<211> LENGTH: 272
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 439

caacctctta caaccaggc attcctttct atcgataatt actctttcaa ccaattgcc          60
atcagaaaaat tgttatatct acctataatc tagaagcccc cacatcaagt tgttttgcc          120
ttctggacag gaccaatgta tatcttaaatt gtatttgatt gatctctcat gtctccctaa          180
aatgtataaaa accacgctgt tccccgacca cctgggagcac atgttctcag ggtctcctga          240
gggctgtgtc acaggccatg ttcacttaca tt          272

<210> SEQ ID NO 440
<211> LENGTH: 189
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 440

ccctgcagag aatcacgtcc tggaactgca tgttcttgcg actcttggga cttcatttta          60
actttctgct gccccagcca tgttttcaac catggcatcc ctcccccaat tagttccctg          120
tcatectcgt caaccttctc tgtaagtgcc tggtaagett gcccttgctt aagaactcaa          180
aacatagct          189

<210> SEQ ID NO 441
<211> LENGTH: 163
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 441

tgagcagact gcaccccaag ctcccgaact caggteccct gatettgggg cctgtttccc          60
atgggattca agagggacag cccagcttt gtgtgtgttt aagcttagga atcgcttta          120
tggaaggggc tatgtgggag agtcagctat cttgtctggt ttt          163

<210> SEQ ID NO 442
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (75)..(75)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (262)..(262)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 442

atgggtgtag atcaaggcag gacgaggaac caaaaagaaa ggcataaaca taagaaaaaa          60
aatggaaggg gtggnaaaca gagtacaata acatgagtaa tttgatgggg gctattatga          120
actgagaaat gaactttgaa aagtatcttg gggccaaatc atgtagactc ttgagtgatg          180

```

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tgттаaggaa tgctatgagt gctgagagg catcagaagt ccttgagagc ctccagagaa 240

aggctcttaa aaatgcagcg cnatctccag tgacagaaga tactgctaga aatctg 296

<210> SEQ ID NO 443

<211> LENGTH: 246

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 443

gttacagatt caagcaatgg atgcaaggaa catgctgtat gtaatagaag aaagaagtcc 60

acgttttcgg cagaagtagt gagtcagtgt ggaagagagg tgagggtgtg ctttactttt 120

tgataaagag aaagatgttt actcataaac ccttcaaaag gtattaacaa atgtttacca 180

aacctattgc tttattttta aaacataatt tgtgttttct atttgtaaga tctgacattt 240

cgaggc 246

<210> SEQ ID NO 444

<211> LENGTH: 121

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 444

ggcagcgacc cggaacagc gtatcactga gaccgagtcg ccttatcagg agctccaggg 60

tcagaggtcg gatgtctaca gcgacctcaa cacacagagg ccgtattaca aatgagcccg 120

a 121

<210> SEQ ID NO 445

<211> LENGTH: 262

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 445

tggtgaccag ttctcggttt catagttttt actatcagtt tgcctttggg attctttgaa 60

agctcttgag gctttttccg cagcttctag gagatgtgtt aggtcattaa cagtaatgct 120

cctacagttt ttgttcccat ccaaccacca tttgatttca cttttgtaga cttgacctag 180

tgtatctgaa atataggaat ttttaggtgc tttcattttg gcctgacgtg cccagtcag 240

agctgtgtta aagtccttct ct 262

<210> SEQ ID NO 446

<211> LENGTH: 226

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 446

gtcattcaca actgatttca agagtcacct tcaccaggaa gtcttccttg accaccatca 60

ttcctgcctg attagagggc ttctcatggt taatatgtgt tctcaagttt tcagtgtcaa 120

ggaatgccat ccagaagct cattttcaga tgcacaacag ccagaacagt ctcaagcagc 180

attctagagc ttggaattta agaactacgc attgcctata aagtga 226

<210> SEQ ID NO 447

<211> LENGTH: 272

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 447

```
agagctcttg agtgggctag tgactcccc tgcagcctgg tggagatggg gtgaggagcg      60
aagagccctc tgctctagga tttgggttga aaaacagaga gagaagtggg gagttgccac      120
aggagctaac acgctgggag gcagttgggg gcgggtgaac tttgtgtage cgaggccgca      180
ccctccctca ttccaggtc attcattttc atgctccatt gccagactct tgctgggagc      240
ccgtccagaa tgctctccca ataaaactcc at                                     272
```

<210> SEQ ID NO 448

<211> LENGTH: 151

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 448

```
tagggattaa cttctgtgat gctgcaactc atgaacttgg ccattctttg ggtatgggac      60
attcctctga tcctaagtca gtgatgtatc caacctatgg aaatggagat ccccaaaatt      120
ttaaactttc ccaggatgat attaaaggca t                                     151
```

<210> SEQ ID NO 449

<211> LENGTH: 243

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 449

```
tccccgtctt gaacactgaa gggcagggtgg tgggccatgg ccatggtecc cagctgagga      60
gcaggtgtcc ctgagaaccc aaacttccca gagagtatgt gagaaccaac caatgaaaac      120
agtcccatcg ctcttaccgg gtaagtaaac agtcagaaaa ttagcatgaa agcagtttag      180
cattgggagg aagctcagat ctctagagct gtcttgctgc cgcccaggat tgacctgtgt      240
gta                                     243
```

<210> SEQ ID NO 450

<211> LENGTH: 82

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 450

```
cagatgttgg tatctgcagg gatcctggaa ccaaaccctt gcagatacta agggctgacg      60
atctaggtaa gactggatatt aa                                             82
```

<210> SEQ ID NO 451

<211> LENGTH: 236

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 451

```
actctcaggc tgcgtccagc gacagtgcc agggtcttga tgtgtctctc acagcttgaa      60
aagcctgaga cagctgtctt gtgagggact gagatgcagg atttcttcac gcctcccctt      120
tgtgaactca agagcctctg gcattctctt ctgcaaaggc acctgaatgt gtctgcgtcc      180
ctgttagcat aatgtgagga ggtggagaga cagcccaccc ttgtgtccac tgtgac       236
```

<210> SEQ ID NO 452

<211> LENGTH: 119

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 452
gccagagaga ccaagtgtta tgtaagaagt agtgtcggct gtgtagaacc actgactaca 60
caggccgaag ttactgagaa ctgggacaga aaaaatagcc agcaagtgtt caaactact 119

<210> SEQ ID NO 453
<211> LENGTH: 264
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 453
gccaacagca tcttttccgg gttcctgtct tttccagata tggaggcctg acctgtgggc 60
tgcttcacat ccaccccgcc tccccctgcc agcaacgtct actctacccc caacaccacc 120
ccttgcccag ccaatgcaca cagtagggct tggatgaatgc tgctgagtga atgagtaaat 180
aaacttttca aggccaaagg acagtgggtt aattcaactc tgtgtcccag cacctggcac 240
accagaagtg ccatgtctag aaat 264

<210> SEQ ID NO 454
<211> LENGTH: 273
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 454
ttcaaaactca atgatgtctac catgcctctc caacattttc aacccctga cattatcttg 60
gatcctatgg tttctccatc caattctttg aatttccag tctccctat gtaaaactta 120
gcaacttggg ggacctcatt cctgggacta tgctgtaacc aaattattgt ccaaggtat 180
atttttggga tgaatataat ttgaggaagg gagttaaga ccctcctggg gctctcagt 240
tgccatagag gacagcaact ggtgattgtt tca 273

<210> SEQ ID NO 455
<211> LENGTH: 275
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 455
acttacatag tagcttccaa ggacaggtgg aggtagggcc agcctggcgg gaggaggagaa 60
gcccagtcgt tcctatgtaa gggacaaagc caggtttaat ggtactgggt agggggcact 120
gccaagacaa taagctaggc tactgggtcc agctactact ttggtgggat tcaggtgagt 180
ctccatgcac ttcacatgtt acccagtgtt cttgttactt ccaaggagaa ccaagaatgg 240
ctctgtcaca ctggaagcca ggtttgatca ataaa 275

<210> SEQ ID NO 456
<211> LENGTH: 261
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 456
tcaactccac ctgttactgc tgggagtc aa gtcagctagg aaggaagcag gacatttttt 60
caaacagcaa gtggggccca tggaaactgaa tctttactcc ttggtgcacc gcttttgctg 120
tgcgttgctt tgctccgttt ttcccaaaaa gcactggctt catcaaggcc accgacgatt 180

-continued

tccctgagtgc actgggaaat ttgggtatag gtcaggcttg gcagccttga tcccaggaga 240

gtactaatgg taacaagtca a 261

<210> SEQ ID NO 457

<211> LENGTH: 241

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 457

ttgttcccga ctagctgctt tgcacattat tttcattttc ctggaatttg atacagagag 60

caatttatag ccaattgata gcttatgctg tttcaatgta aattcgtggg aaataactta 120

ggaactgcct tttctttttc ttgaaaaacc tacttataac tgttgctaata aagaatgtgt 180

attgttcagg acaacttgct tccatacagt tgggttgtaa ccctcatgct tggcccaaat 240

a 241

<210> SEQ ID NO 458

<211> LENGTH: 107

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 458

taaatataat atcgacacag tgetttccgt ggcactgcat acaatctgag gctcctcttc 60

tcagttttta tatagatggc gagaacctaa gtttcagttg attttac 107

<210> SEQ ID NO 459

<211> LENGTH: 252

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (180)..(182)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 459

gtggagcagt tggactgctc tctctgctct caggatgata ctgtgagaac aatttaaata 60

tgctaagcac atgtcaggaa acagttttgt ggtcttttga cactcgtgtg agccattccg 120

ttccatttca ggtgatttta ttcatttcat ttgtagaata aaataaatcc atttcacacn 180

nncacacaca cacacacaca cacacacaca caccctctat acaccactaa agcctcccat 240

taaaccata ga 252

<210> SEQ ID NO 460

<211> LENGTH: 96

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 460

tcgacacagt gctttccgtg gcactgcata caatctgagg cctcctctct cagtttttat 60

atagatggcg agaacctaa gtttcagttga ttttac 96

<210> SEQ ID NO 461

<211> LENGTH: 181

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

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<222> LOCATION: (43)..(44)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (78)..(79)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (99)..(99)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (110)..(110)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 461

gccagagaag cgattagaaa ccctgaggg ccgattactg acnncataaa tcatgagttt	60
gggggctttg cctgggtntt gttggtacca ggagacatng ttataaccan caacgtcact	120
gctggttcca gtgcaggaga tggatgatga ctgtccagga gaccagaca cggaggcagg	180
c	181

<210> SEQ ID NO 462
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 462

aggagctgag gtgctaccg gagccccatt cccccacc tgcccacttg ggaatctgag	60
gcagaggagg gtgaggcctg tgtgccaacc ttgttcacat accaccttcg tcccc	115

<210> SEQ ID NO 463
<211> LENGTH: 53
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 463

aagcaagata tcaatgtagc agaattgcac ttgtgcctca cgaacataca taa	53
--	----

<210> SEQ ID NO 464
<211> LENGTH: 155
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 464

gttgttgatc atggatcata ctccccttgt ttctttgggt gagaagggat cgcagtttgg	60
aaactccggc ggctgcgtgc ggggtttcag tcccagctgt aggcttgtaa ataccgccc	120
cgccaaaccg catagagaac gtggcagcaa gctga	155

<210> SEQ ID NO 465
<211> LENGTH: 190
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 465

cacagggaaa tcagggttac aaattcttct gatccacttc tctcaggatc cctctcttc	60
ctacccttcc tcaccacttc cctcagtcct aactcctttt cctatttcc ttctcctct	120
gtctttaag cctgcctctt ccaggaagac cccctatttg ctgtggggc tccccatttg	180
cttactttgc	190

-continued

<210> SEQ ID NO 466

<211> LENGTH: 63

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 466

attagaacct tagtataaat ttactttctc aaattcttgc catgagaggt tgatgagtta 60

att 63

<210> SEQ ID NO 467

<211> LENGTH: 281

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 467

ggagacagat ggagggtacc ctatttacia ctgagtcagc caagccactg atgggaatat 60

acagatttag gtgctaaacc atttatttct cacggatgag tcacaatttg aagaatcaaa 120

cttccatcct gaaaaattat atgtttcaaa accacttgcc atcctgttag attgccagtt 180

cctgggacca ggcctcagac tgtgaagtat atatcctcca gcattcagtc cagggggagc 240

cacggaaacc atgtttttgc ttaagccatt aaagtcagag a 281

<210> SEQ ID NO 468

<211> LENGTH: 239

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 468

agatgcgctc gagaccacg ggccttcac ctccctcagc ttctgcatg gaccacactt 60

actggccagt ctgcatcctt gcttagacca ttctccctc cagggagccc accctgacct 120

acccccactg cccccctcc ccatgggttc ttctcttct ctgaacttct ttaggagtca 180

ctgcttggtg ggttcctggg acacttaacc aatgccttct ggtactgcca ttctttttt 239

<210> SEQ ID NO 469

<211> LENGTH: 196

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 469

gcctttaaga taccttgatg aagacctgga ctattgaatg gagcagaaat tcacctctct 60

cactgactat tacagttgca tttttatgga gttcttcttc tcctaggatt cctaagactg 120

ctgctgaatt tataaaaatt aagtttgatg atgtgactac ttagtggtgt atatgagact 180

ttcaaggga ttaaat 196

<210> SEQ ID NO 470

<211> LENGTH: 38

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 470

agtctgccta tgatctttga atgagctttt taaggaag 38

<210> SEQ ID NO 471

<211> LENGTH: 110

-continued

```

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 471

ttaaacttga ggggtgtagag gtctctccacg cttgtttgcc tgaaagtaat ataatgatgc      60
tgtctgaaca ggtttttactg cttgctttcc aagtaaaggt taattatgat                    110

<210> SEQ ID NO 472
<211> LENGTH: 173
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 472

tattttccct ctttcgaaca aagacattgg ttgcccag gactacaaat aaaccaacgg      60
gaaaaaaagaa aggttccagt ttgtctgaa aattctgatt aagcctctgg gccctacagc     120
ctggagaacc tggagaatcc tacaccaca gaaccgggt ttgtcccaa aga                  173

<210> SEQ ID NO 473
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 473

gttatttaag atggctatcc agataatcct gaacactgtg tatttatattt atttagacta      60
ccagcaaaga ttaaagcatg aa                                                  82

<210> SEQ ID NO 474
<211> LENGTH: 266
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 474

gcttgggggaa caatgatggg gcacaaaggc ttagatttgc cttgtctcaa aataaggaat      60
tttgtagtgg ttttcaaaaa taattcaaca aagaacaat acaaaaagtg ggtagaatta     120
cctatcacat ttcccaatct tgactattca gaatgctgtt tatttagtga tgaggattag     180
cacttgattg aagattcttt taaaatacta tcagttaaac atttaatatg attatgatta     240
atgtattcat tatgctacag aactga                                             266

<210> SEQ ID NO 475
<211> LENGTH: 115
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 475

cagaaagcca agtggactca acggagaggc cagcaagttt caggaaatgg tgcatttggg      60
gaacaaggag tcgtcagaaa ctccagacca gtttatgaca gctgatgaga caagg          115

<210> SEQ ID NO 476
<211> LENGTH: 262
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 476

gttcacccgg tgaactatth atgagttctt ttggtgtgaa gaaagggctc atgttgcaatt      60
tccagccatt gctacaaaaga acctttatth gtccagtaac ggtagaaaaat ccttcccgat     120

```

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taaaaacttc agacttgctg aatatcctgc aatgtcaaga tgaccgatgt tgagttgggt 180
ggatttgcta acgagtcaga ttgaacatg aggctattgg aacccaatag gcgtcattga 240
tggcggcaag ccatagcttt ca 262

<210> SEQ ID NO 477
<211> LENGTH: 94
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 477

ggggagccag gcttcctca cgcagcctgt ggtggatgtg ggaaggagat caacttctcc 60
tcactctggg acagacgatg tatggaaact aaaa 94

<210> SEQ ID NO 478
<211> LENGTH: 114
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 478

ctgcacagct cagcacaaca ttccaagtc aaaatagaag ccttctcagt gagctccagc 60
acgcccagag gactgttaat aacgatgac catgtgtttt actctaaagt gcta 114

<210> SEQ ID NO 479
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 479

cagggactgg ctatccaag acctggcaga tgtggct 37

<210> SEQ ID NO 480
<211> LENGTH: 74
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 480

gtgaaagga agtagaacg aaacaagatt agtcctgagt taacaatggc tgcaagctgg 60
atacatggaa ttca 74

<210> SEQ ID NO 481
<211> LENGTH: 201
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 481

tggtgaatgc gtgctgccca ggaccagtga agacagacat ggatgggaaa gacagcatca 60
ggactgtgga ggagggggct gagaccctg tctacttggc cctcttgcc cagatgccca 120
ctgagccaca aggccagttg gtccatgaca aagttgtgca aaactggtaa acgtctgctt 180
cggagcttgc tgcttaataa a 201

<210> SEQ ID NO 482
<211> LENGTH: 217
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 482

-continued

atgctgtggt tggatcaagg actcattcct gccttggaga aaatacttca accagagcag 60
ggagcctggg ggtgtcgggg caggaggctg gggatggggg tgggatatga ggggtgcatg 120
cagctgaggg cagggccagg gctggtgtcc ctaagggtgt acagactctt gtgaatatTT 180
gtattttcca gatggaataa aaaggcccggt gtaatta 217

<210> SEQ ID NO 483
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 483

ttctgtgcct cagccgttct tgacatcaag aat 33

<210> SEQ ID NO 484
<211> LENGTH: 222
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 484

gacacagtcg ggttgaccca gggctgtctc cctccagagc ctccctccgg acaatgagtc 60
ccccctcttg tctccacccc tgagattggg catgggggtg ggtgtggggg gcatgtgctg 120
cctgttgtta tgggtttttt ttgcgggggg ggttgctttt ttctgggggc tttagactcc 180
aaaaaataaa cacttccttt gagggagagc acaccttccc aa 222

<210> SEQ ID NO 485
<211> LENGTH: 278
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 485

tgagaggcaa gagttgttcc tgcccttccc tttgtgactt gaagaacct gactttgttt 60
ctgcaaaggc acctgcatgt gtctgtgttc gtgtaggcat aatgtgagga ggtggggaga 120
gcacccccc cccatgtcca ccatgacct ctccccacgc tgacctgtgc tccctctcca 180
atcatctttc ctgttccaga gaggtggggc tgaggtgtct ccatctctgt ctcaacttca 240
tggtgcactg agctgtaact tcttccttcc ctattaaa 278

<210> SEQ ID NO 486
<211> LENGTH: 199
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (113)..(113)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (115)..(115)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (122)..(122)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 486

aaggagagcc ggaggatggg ctgcagctgt ggaggaggtt ttcagaggag agaggtcgga 60
gagcagaggg ctgagaagcc agaggcaggt ggagagaggg tggaaagtga gcntnagcgg 120

-continued

 gncttgggct ggagccgcac acgctctcct cccatgttaa atagcacctt tagaaaaatt 180

cacaagtccc catccacat 199

<210> SEQ ID NO 487

<211> LENGTH: 168

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 487

aagaaaagga gaagcactac aagcttttga aaaatggaaa gagaaaaaga tggaatatct 60

taaagagaaa aatagaaagg agagagaata tgaaagagca aagaaacaga aagaggagga 120

aactgttgcc gagaaaaaga aagataattt aactgctgtt gagaaatg 168

<210> SEQ ID NO 488

<211> LENGTH: 66

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 488

ggagaaccac cccacccccca atgtccacca tgacctctt cccaacgctg aacctgtgct 60

ccctcc 66

<210> SEQ ID NO 489

<211> LENGTH: 185

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 489

ttgacaggtg ggcccagtga acttttccag taaatgaagc aagcactgaa taaaaacctc 60

ctgaactggg aacaaagatc tacaggcaag caagatgccc acacaacagg cttatatttct 120

gtgaaggaac caactgatct cccccacct tggattagag ttctgtctct accttaccca 180

cagat 185

<210> SEQ ID NO 490

<211> LENGTH: 160

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 490

gaaaatgggc tcttgacacc aacattgaaa gcaaagcgag gagagcttcc caaatacttt 60

cggacccaaa ttgacagcct gtatgagcac atccaggatt aggataaggc acttaagtac 120

ctgccggccc actgtgcact gcttgtgaga aaatggatta 160

<210> SEQ ID NO 491

<211> LENGTH: 239

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 491

aagaacaact cctcaccagt tcctcctgag gctgggagga ccgggatgct ggattctgtt 60

ttccgaagtc actgcagcgg atgatggaac tgaatcgata cgggtgtttc tgtccctcct 120

actttccttc acaccagaca gccctcatg tctccaggac aggacaggac tacagacaac 180

tctttcttta aataaattaa gtcttttaca taaaaacaca actgcaaagt accttcata 239

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<210> SEQ ID NO 492

<211> LENGTH: 244

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 492

```
cactcccgagg actattgccg agaaggggca agggatgagt caagaagggtg agacccttcc      60
cggtggggcac gtggggccagg ctgtgtgaga tggttgatgt ttggtactgt ccatgtctgg      120
gtgtgtgcct attacctcag catttctcac aaagtgtacc atgtagcatg tttgtgtat      180
ataaaaggga ggggtttttt aaaaatatat tcccagatta tccttgaat gacacgaatc      240
tgca                                             244
```

<210> SEQ ID NO 493

<211> LENGTH: 192

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 493

```
agatcatccg ccagcgggaa caacgcgttg gagctctccc agctggagta acagatcctg      60
gaaccaacag ccgacatggt gcaccttgcc cgcaagtaca aggaccctgg agcacaagtc      120
cccgcccttg ggccatttgg cccccaaccc aatcaaaaat ctttccccc ccttgaggaa      180
gcactgcccc aa                                             192
```

<210> SEQ ID NO 494

<211> LENGTH: 214

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 494

```
ggatcttgat gcctgaaaat cccaagattg gtacttggca aactgaaaga aatctagaaa      60
accctagaga tcaggcatct gtggccagct aactggatcat acaaatggat tgttgtggtg      120
aacttgata gtattaatcc tgagatgctg tccccctcca cccccacccc cacaaaaaaa      180
ataaataaag tagtattaag ttagcctcat acaa                                             214
```

<210> SEQ ID NO 495

<211> LENGTH: 164

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 495

```
ccatggcaat gcgggtgact cctttacatg gcacaacggc aagcagttca ccaccctgga      60
cagagatcat gatgtctaca caggaaactg tgcccactac cagaaggagg gctgggtgta      120
taacgcctgt gccactcca acctcaacgg ggtctggtac cgcg                                             164
```

<210> SEQ ID NO 496

<211> LENGTH: 249

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (128)..(128)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 496

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attgactatt gactcgtgca tagaatccaa tgctgtaatt agaaagtaat ctgtgactag	60
aatagacctt tgtccctggt agtagccctg ttgccatggt caggetttta aaaaatgctt	120
ttgtgtcncc aaatatatct ataaagaaaa caaaatttct gtccagaggc ctctgaaact	180
tggttttctt acatgtgggt ggtttatgtg acaatcccta tgaaatgagt ggacgtatga	240
tttttgaat	249

<210> SEQ ID NO 497
 <211> LENGTH: 270
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 497

ctctcttctt tcttcttatt gactactgtg cagactcagc tggatttttag ataactctta	60
taatatcaca atggtttcca tggagatgga tcatgatgtc acaaaagtag atatatattc	120
tttgatactt gaaaaatcaa agggcaatag agggaggaag agaagaattt tcaaactggt	180
atatagagga gggggaaatc tagagaacag gaaagaaaac taagaaaggg tgtgagtga	240
acagagaaat ggctattcaa aggcatttca	270

<210> SEQ ID NO 498
 <211> LENGTH: 256
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 498

tgtggaccag aaacaggcca ctctccctgc tgcagggtgt gcttagcaat caaaaagcaa	60
atcctctttc taactgggct gtgccacagt taaagtttca taaacctaac catgctctgc	120
ccaccttttag aggaggaagt taaactcagc cctaaaaaaa ttatagaaaa gtacacatct	180
gctaataaaa ttggttgata tggattttca ataaaggctc agtttaaaaa ccagcgctta	240
aggcagtata atctct	256

<210> SEQ ID NO 499
 <211> LENGTH: 229
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 499

ataggggcct caattcagcc cttgacagtg tggttcagga atgcagttcc aaaatacact	60
catgttacct aagccttgag ttctcaggt gggcctctga gggccagcag ggaagacaag	120
gtcagccagc tttaggttg ggtgtggact tgggtggccac cattactagt ttaataagat	180
cttactggtg gcttaggcaa gttggctgtt cctcaggagg ttattggca	229

<210> SEQ ID NO 500
 <211> LENGTH: 210
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 500

cctcacattg aggaacactg cttatcaaga gtttcaggag accccaacgt tgagaattca	60
gttctgagcc atcccaactt cttaggattg ttgtgcggtg gttaaaactt tcttgtaag	120
agtttttgag atctttggac gaaaggtttc tggataaatt tatatcacia attagtaagg	180

-continued

gtttcatagt aagtggtt tcttttcct 210

<210> SEQ ID NO 501
<211> LENGTH: 289
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 501

aacagtcatt ctgtcgttat ccaccaatt ttcaaatca agcccatgt aaatagtcatt 60
ttccataaat cctgtcaaga aaattaattt ttaggtaca gtcattggtt ttattgtagt 120
cctcctaatt ctgtgtgaca tagatccttt ggaaagtgg tgctaccagt tgggaagtgc 180
cccagcaggc cccgtggttg tctggctttg ttgactgtct gaatgcaaca cgttgacaat 240
gggttagctg ctttggtttt aggggttatt tcttatgcc tcatgcaaa 289

<210> SEQ ID NO 502
<211> LENGTH: 198
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 502

aaatcctctt tctaactggg ctgtgccaca gttaaagttt cataaaccta accatgctct 60
gccacacctt agaggaggaa gttaaactca gccctaaaa aattatagaa aagtacacat 120
ctgctaataa aattggttga tatggtattt caataaaggc tcagtttaaa aaccagcgct 180
taaggcagta taatctct 198

<210> SEQ ID NO 503
<211> LENGTH: 172
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 503

gttaacttac ttaagtcatt gtcgaagaa agatcaaacc catgaatgct tagtagctaa 60
ggctagtgtt caaaagcact ttaaaagaca tttgtccac attttgaaa agaaaatatt 120
tgcatgttta attcataatt taggctatct ttgagtatac tgtaaagtgc tg 172

<210> SEQ ID NO 504
<211> LENGTH: 220
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 504

aaggataaac aaggcctgctg tccagacaga gttgtttctc tgaaacattg ctggcttctt 60
ctgagtttga ttcagctgtt ctctgatgaa attcaggga aacttgccct cagagatatc 120
tctcaaattt tactaatctt cagctttagt tggccaacat tcattccaca aatatcaatt 180
gaactcctac tgtgggcctg gtggtggtct gagtgtgaa 220

<210> SEQ ID NO 505
<211> LENGTH: 205
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 505

aacaaagtta tgttctagta tggttttaa agtcttcctt tttggttatt tggaaaatag 60

-continued

tgcaaacgtg cggtctagtg gttatggcca aaggcagagc aaaggagtg cggccttagc	120
cagccccagc cagctgccat tgctcccacg ctctgtgtgg tcttgacca atgccagaa	180
aagcaagggt cccactttc tacct	205

<210> SEQ ID NO 506
 <211> LENGTH: 177
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 506

aattcacttg gctgcaaac aacagagtta tccgtathtt ccacatgtga atgtcattgc	60
aagggtgact ctagacaaac taaaaaccga tggaccgtca agctcccag gagccccctg	120
gatggcagcg ttgcttcaga gtgtttcctg tttctggaat tccttgtag ggaactt	177

<210> SEQ ID NO 507
 <211> LENGTH: 168
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 507

cagctttcag acagagccca cttagcttgt ccacatggat ttcaatgcca atcctccatt	60
ttctctctcc agatathttt gggagtgaca aacattcttt catcctactt agcctaccta	120
gatttttcat gacgagttaa tgcattgtccg tggttgggtg cacctgta	168

<210> SEQ ID NO 508
 <211> LENGTH: 42
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 508

tcatgacgag ttaatgcatg tccgtgggtg ggtgcacctg ta	42
--	----

<210> SEQ ID NO 509
 <211> LENGTH: 250
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 509

gattttctcat gacgagttaa tgcattgtccg tggttgggtg cacctgtagt tctgtttatt	60
ggtcagtggg aatgaaaaaa aaaaaaaaaa aaagtctgcy ttcattgcag ttccagtttc	120
tcttccattc tgtgtcacag acaccaacac accactcatt ggaaatgga aaaaaaaaaa	180
aaaaaaaaaa caaaaaaatg tacaatggat gcattgaaat tatatgtaat tgtataaatg	240
gtgcaacagt	250

<210> SEQ ID NO 510
 <211> LENGTH: 225
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 510

ttctttcttg cccagttaat ttgcacagaa cttttctcag tttggathtt ttactgctt	60
ggagatccag aagagaatta gaaacaacat agcaaattaa aataggtttg tcaataatag	120
agctcagaca cctgtgtgct gtagattcac atacaggccg tgaacctaa tggggaaaat	180

-continued

cctacctatc caccttctgg ctagattacc tagcttagtg aaaag 225

<210> SEQ ID NO 511
<211> LENGTH: 210
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 511

cctacagaca cccatcggtt gggtaggagg aacagatttg agaaatgggc aggagatgta 60
ggaggggaac taggttaccg cttatcagat ggcataaatt ttcaaggaga atcaaaatgc 120
aaaacttggg aataaatcat agcaatatca taattaatgt agtagtaata ttgctgttta 180
ttaatgctga agtgtgggtt tcctaactgt 210

<210> SEQ ID NO 512
<211> LENGTH: 197
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 512

gggatgtacc tgaaacctag tgagagtcac cctgactctg gggaagagcc gttcaaagat 60
gagaaagata aagtaatttg ccaccccaaa cccctcacag gctagactat ccatggattt 120
cagtggggtg gtgagtcctc atgatccctg aacctctcct caaatgggtga ctgttctggg 180
ggtcctttct ctgcctt 197

<210> SEQ ID NO 513
<211> LENGTH: 261
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 513

tcttttccat acactgtgtg ctatttgtgt taacatggaa gaggattcat tgtttttatt 60
tttatttttt taattttttc ttttttatta agctagcatc tgccccagtt ggtgttcaaa 120
tagcacttga ctctgctctg gatattctga tcttttctct aatcagagat acagagggtt 180
agtataaaat aaacctgtct agataggaca attaagtgca ctgtacaatt ttcccagttt 240
acaggtctat acttaaggga a 261

<210> SEQ ID NO 514
<211> LENGTH: 253
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 514

gggcattcaa agttatcctt tggataatga tgatttaaaa ctttctttta ttatcccatg 60
tgctcagagt aaggggcaaa tgaatcagtt gtgaaatatg tgttccttgt aggacacagg 120
cactcttgag atctatagct tcaataaaaa ggtaatttat ttaaattact gcctctttaa 180
tttataatgt tttggggatt ttttaataggc atgctctgta agggcactgg taatcagctg 240
tttctgattt tac 253

<210> SEQ ID NO 515
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 515

tgctgtaatt aagaaagcag tgtaaggctg ggcgcagt 38

<210> SEQ ID NO 516

<211> LENGTH: 219

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 516

atgtctcgcc gcaagcaagg caaaccccaa cacttaagca aacgggaatt ctgcccagag 60

cctcttgaag ccattcttac agatgatgaa ccagaccacg gcccgttggg agctccagaa 120

ggggatcatg acctcctcac ctgtgggcag tgccagatga acttoccata gggggacatt 180

cttatttttta tcgagcacia acggaacaaa tgcaatggc 219

<210> SEQ ID NO 517

<211> LENGTH: 253

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 517

agcctaggcc tgcagcgcca ttttatttat attttttaat aaaaagtaaa aacaaaaaaaa 60

cagaccaca ttggaacagt gaatcagtc catagagagg gcccgtaggac catcgctgtc 120

atgagtgatg ccttgccctt tttgaaacca gccaacctaa ttacctgtat tgtggaaatg 180

cgcatgagtc cccaaccctt tgtttctata cattctatgt tgtcttttaa aaagtgtgct 240

taacattgac aca 253

<210> SEQ ID NO 518

<211> LENGTH: 298

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 518

tttagcatct tggagccgtg tcagctgcag agactggagt ccggggcatg atggggatgt 60

acctgaaacc tagtgagagt catcctgact ctggggaaga gccgttcaaa gatgagaaag 120

ataaagtaat ttgccacccc caaccctca caggctagac tatccatgga ttccagtggg 180

gtggtgagtc ctcgatgacc ctgaacctct cctcaaatgg tgactgttct gggggtcctt 240

tctctgcctt tctcaggggg taaccagagg tgggtggtgtg gtccactgtg actcgtca 298

<210> SEQ ID NO 519

<211> LENGTH: 259

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (143)..(144)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 519

aatgaaagct gtttgcgta acttgaaatt ttatctttta ctatgggagt cactatttat 60

tattgccttat gtgccctgtt caaaacagag gcaacttaatt tgatctttta tttttctttg 120

tttttatttt tttttttatt tanntgacca aaggtcatta caacctggct ttttattgta 180

tttgtttctg gtctttgtta agttctattg gaaaaaccac tgtctgtgtt tttttggcag 240

-continued

ttgtctgcat taacctggt 259

<210> SEQ ID NO 520
<211> LENGTH: 192
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (135)..(135)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 520

tgggactaga ggaaggactt aaactcatac ctaacttcac cttttgatct tgatgccct 60
gggtgtgtag tgccagtcct gagcccttg tcatggggcc tttcctgtac cctcaggacc 120
cctgactcat ggctncccca ccccccaacc ccatgccatt gccaatctc taaatgcatt 180
cacaacaca aa 192

<210> SEQ ID NO 521
<211> LENGTH: 136
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 521

tgcattcttc caatttaaga ggtataaaat agtccttcga tgtgggtttt attttgctt 60
tctttgactg tgaatgacct tggccatttc ctcatattt ttggttattg tatttgact 120
tgcacacctt gtctct 136

<210> SEQ ID NO 522
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 522

aggtgatgcc tggcttgaca cttctggtaa etc 33

<210> SEQ ID NO 523
<211> LENGTH: 243
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 523

aggattgagc gcaggagca aatcattcag gaaatatgga tgaacagtgg ttgggacacc 60
tcgctcccaa gaaacatggg ccagttttac tgaaaaccac atgcatcttg atgcatcg 120
actttttgaa gaaggaagga tcccaaatgc cctccagtt ttggttcacc tgtaccttct 180
atgaaggaga attcgtcatg tcattcaaca ctctgaggc caggaagcta ttaaagggat 240
gtt 243

<210> SEQ ID NO 524
<211> LENGTH: 174
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 524

aaacaaaaca aaaggctggg cgcggtgact cacgcttgta atcccagcac ttggggaggc 60
ctaggcaggc agatcacctg aggccaggag ttcgagacca gcctggccaa catagtga 120

-continued

gtctctacta aaaatacaaa aattagccgg atgtggtggc agtcacctgt aatc 174

<210> SEQ ID NO 525
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 525

cagcctccaa cacaaggctc caagacctag gctcatggac gagatgggaa g 51

<210> SEQ ID NO 526
<211> LENGTH: 208
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 526

ttggccttgg cttttctagc ctatttacct gcaggetgag ccactctttt ccctttcccc 60

agcatcactc cccaaggaag agccaatgtt ttccacctat aatcctttct gccgacctct 120

agttcccttt gctcagccaa gcttggtatc agctttcagg gccatgggtc acattagaat 180

aaaaggtagt aattagaaca ctttgcaa 208

<210> SEQ ID NO 527
<211> LENGTH: 211
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 527

accgaaagta ctgaccaagt gccaggaaga ggtcagccac atccctgctg tccaccggg 60

ttcattcagg cccaagtgcg acgagaacgg caactatctg ccactccagt gctatgggag 120

catcggttac tgctggtgtg tcttcccaaa cggcacggag gtccccaaca ccagaagccg 180

cgggcacccat aactgcagtg agtcactgga a 211

<210> SEQ ID NO 528
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 528

caagacctag gctcatggac gagatgggaa ggcacaggga gaagggataa ccctacacct 60

agaccccagg ctggacatgc tgactgtcct ctcccctcca gcctttgggc ttggcttttc 120

tagcctatctt acctgcaggc tgagccactc tcttcccttt cccagcctc actcccaag 180

gaagagccaa tgttttccac ccataatcct ttctgccgac ccctagtctc ctctgctcag 240

ccaagcttgt taccagcttt cagggccatg gttcacatta gaata 285

<210> SEQ ID NO 529
<211> LENGTH: 224
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 529

tcagtgcacg atgtccagc cacactggcc atctttcggt tctgatata aaaaaaaca 60

cgttcctttt ccatggaag caggtcacc ttgttatctt gtatcgatga caactcttta 120

aacttatctt gctttttggc tttatgtatg tgtgtgggtg ggtgggactg actgccccac 180

-continued

tagaatgtaa gctccatgag ggcaggaat cttgctttct tggt 224

<210> SEQ ID NO 530
 <211> LENGTH: 267
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 530

```

ggaggcagac aatgacccca cggctcctcc ttatgactcc attcaaatct acggttatga    60
aggcaggggc tcagtggcgc ggtccctgag ctccctagag tcggccacca cagattcaga    120
cttgactat gattatctac agaactgggg acctcgtttt aagaaactag cagatttgta    180
tggttccaaa gacacttttg atgacgattc ttaacaataa cgatacaaat ttggccttaa    240
gaactgtgtc tggcggttctc aagaatc                                     267

```

<210> SEQ ID NO 531
 <211> LENGTH: 257
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 531

```

ttgttactgc tgattcttgt aaatcttttt gcttctactt tcatcttaaa ctaatacgtg    60
ccagatataa ctgtcttggt tcagtggag agccctatt tctatgtcat ttttaatgta    120
tctatttgta caattttaaa gttcttattt tagtatacgt ataaatatca gtattctgac    180
atgtaagaaa atgttacggc atcacactta tattttatga acattgtact gttgctttaa    240
tatgagcttc aatataa                                           257

```

<210> SEQ ID NO 532
 <211> LENGTH: 256
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 532

```

actgcattgc tggacctctc gtgaaactga agccttctct acctgttttt atctcaagtg    60
aacctggaga agcaacaata atggaccttc tccctagtc aaatagcctg tggacctccc    120
ctcatagtca gtctccaaaa acatgtatct ggaattaatt tattacaaag agaagtttag    180
tgtttctctc tttttacatg cgctcaatac tgactactgg ccagacacag caccatcctc    240
ttacaaacat catttc                                           256

```

<210> SEQ ID NO 533
 <211> LENGTH: 260
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 533

```

cttgaacatg ggaaggagtt gttgcagtaa gccaatgtg gccactgtac tccagcctgg    60
gagacagagt gagactctgt ctcaaaaaat gaatgaataa ataaataaat aaataataaa    120
aaagatgatt attaacaatg ccagttaata ttaacaatat taatagtatt atttattact    180
aatgccattt ttctattttt gttaaagtat ttttattatt ttagtttaaa ttattattat    240
gagacaaagg cctccatttc                                           260

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<210> SEQ ID NO 534
<211> LENGTH: 273
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 534

ccttgaaaag cagtgtcaga gcagaattat aaggcatttt taatattccc tgttttaata 60
aaactttttt tatgtttgat ttttttttat attttttgtc cgcacgtata tagatgtgga 120
tacataacat ttaacacggg tgcaatcaga ggggtgatttg atttggttaac ttaatgtcac 180
atcataaaca ttttcatgc tgttatataa tgtacataat catttttaac gactacataa 240
catcccatcc tattgacgaa tcattatgtc ctt 273

<210> SEQ ID NO 535
<211> LENGTH: 240
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (163)..(163)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 535

aagtatacag ctgtaagtaa cctctgcncc atggatgatc cttttctcta ggaatgtatt 60
tggattagag atgacaacta cattttcgca tttttatggt gaagtctttt ttaaaaaggc 120
tgtttacttt tcagtagtta agaatacttg tttttctttt tcnttttttt tttttttaac 180
cttttatttt ttcgttaagc ctctattggt tgtagaacac tcttagaac ttggaaataa 240

<210> SEQ ID NO 536
<211> LENGTH: 221
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 536

ggcagccctg acgtgatgag ctcaaccagc agagacattc catcccaaga gaggtctgcg 60
tgacgcgtcc gggaggccac cctcagcaag accacgcgtac aattggtgga aggggtgaca 120
gctgcattct cctgtgccta ccacgtaacc aaaaatgaag gagaactact gtttacaagc 180
cgccctgggtg tgccctgggca tgcgtgcca cagccatgcc t 221

<210> SEQ ID NO 537
<211> LENGTH: 129
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 537

gatccagaac tgtggctggg caccgtggct cacatctgta atctcatcac ttgggaagg 60
ctaaggcggg tggatcacct aaggttaagga gttcgaaccc agcctttaca atgtaatgaa 120
accctgcct 129

<210> SEQ ID NO 538
<211> LENGTH: 108
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 538

ggtggaagac cagtaattgc tggaagactg gatttgctgg aagacttgat ttactggaag 60
acttggagct tcttgaaga catggattgt ccggaagaca tggattgt 108

<210> SEQ ID NO 539

<211> LENGTH: 45

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 539

ggaggagtga gtccttatgc tgacccaat acttgcagag gtgat 45

<210> SEQ ID NO 540

<211> LENGTH: 106

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 540

tttaggtcag ttaagacgca agcaggaaca gccatgcttc caggattagg aattttactg 60
aatgatccat ggcaccccccac tgcctctgca ggttggtgta atcagc 106

<210> SEQ ID NO 541

<211> LENGTH: 48

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 541

atgttttttta ccaaatgatc ggtagggaga tacaaggga taaagaac 48

<210> SEQ ID NO 542

<211> LENGTH: 70

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 542

cctgccagaa tctgccgccc ctccatcttc tacctctgaa tggccaccct tagaccctgt 60
gatccatcct 70

<210> SEQ ID NO 543

<211> LENGTH: 56

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 543

tcctttgtac tggaggagtg agtccctatg ctgaccccaa tacttgcaga ggtgat 56

<210> SEQ ID NO 544

<211> LENGTH: 223

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 544

caaggtcagc gtaggtaagg atgcaactga aggtcctggg ctgcacctat gctctccagg 60
caacacctcc cactttctac agatcctaca ctccacccat cctcaatgca gccccattcc 120
ttgcacccca gaccagtcag ggatggggga agacgtgaag ttaggaatga cacggggcca 180
gaggcaggaa gctgcccaca aagaggtggt acctactctc cta 223

-continued

<210> SEQ ID NO 545

<211> LENGTH: 106

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 545

tttaggtcag ttaagacgca agcaggaaca gccatgcttc caggattagg aattttactg 60

aatgatccat ggcaccccccac tgcctctgca ggttggtgta atcagc 106

<210> SEQ ID NO 546

<211> LENGTH: 209

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 546

catcctcatg actgatggat tgcacaacat gggcggggac ccaattactg tcattgatga 60

gatccgggac ttgtatataca ttggcaagga tcgcaaaaac ccaagggagg attatttgga 120

tgtttatgtg ttgggggtcg ggcctttggt gaaccaagtg aacatcaatg ctttggcttc 180

caagaaagac aatgagcaac atgtgttca 209

<210> SEQ ID NO 547

<211> LENGTH: 201

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 547

ctcccagtgg attcactgtc cacggcctcc caacatctcc agaccggcca ggetccacca 60

gccccttcgc tccatcagcc actgacctgc ccagcatgcc tgaacctgcc ctgacctccc 120

gagcaaacat gacagagcac aagacgtccc ccaccaatg cccggcagct ggagaggctc 180

ccaacaagct tccaaaatgg c 201

<210> SEQ ID NO 548

<211> LENGTH: 292

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 548

acagtgttgt atgaggtttg aggattttga tccaagctgg tcccactcag tccatagcag 60

agaatgaaag gggccagaga ggggtgtgac ctctgctga agtcacacag tgagtcgagg 120

acagggaggt gaccccaggt ttctatgtgt agggcgggag gatgttttgg gacacagttc 180

aattctcatt tgtcacacac ttgggtatt agagatcaac cccttcgctc ctgtgtcttg 240

caatggcagc cttggcaaac gctaaatgaa aatcgtgaca acacttgtgt ta 292

<210> SEQ ID NO 549

<211> LENGTH: 94

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 549

aattcaaagc gctcagaaag tattagctca ataagtgatg actgtgtgcc agacactgtg 60

ctaaactcct actcaagagg gataagagtc tagg 94

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<210> SEQ ID NO 550
<211> LENGTH: 266
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 550

taacatgttg gctgtcatta ttacatatat ctgtgtttca ttcttgccctc tggttgaat      60
gtttcttccc gctctccata tggtgattt ctcacccctc gggacttgcc ccattctcca      120
accccatcac tagttttatc tttttcactt atttatgcag tctgctcttg tcctaggaca      180
tgagctccag gagggcggga aacatctcgc tttgtacct gctgtgccct ctgtaccag      240
caaggcgctt gtgtataata ggtgct                                266


<210> SEQ ID NO 551
<211> LENGTH: 112
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 551

ggaaaccgga tgagaggaaa gacctggaag ctattgtaa atctatgctg agggctctggt      60
gactactaga ccaagggcat ggcagcagag ggcagctgaa agacttcagg aa            112


<210> SEQ ID NO 552
<211> LENGTH: 90
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 552

gggtttgagt tcataccctg ttaccatttt ggggtaccca ctgctctggt tatctaatat      60
gtaacaagcc accccaaatc atagtggctt                                90


<210> SEQ ID NO 553
<211> LENGTH: 277
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 553

agacaccttg acagggcaca ccgggcactc agaagacact gatgggcaac cccagcctg      60
ctaattcccc agattgcaac aggtgggct tcagtggcag ctgcttttgt ctatgggact      120
caatgcactg acattgttgg ccaaaagccaa agctaggcct ggccagatgc accagccctt      180
agcagggaaa cagctaattg gacactaatg gggcggtgag aggggaacag actggaagca      240
cagcttcatt tcctgtgtct tttttcacta cattata                                277


<210> SEQ ID NO 554
<211> LENGTH: 289
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 554

tccaaatggt cacttttctt cgcaggcctc tctttgcata caaatgtctc cctcctgacg      60
ctcacctttt tccttggggc tctcaaatgt cttcttttca gatttcgtag cttttctttc      120
tttagcatca cttgagggca agtgggtgct caactgtctc cccccagagt tttgccgctt      180
gtactttccc acacctcagt ctctctgctt gtagaaaggg gtcaatcggt tgaaccctgc      240
ttcacttggt gtgtatgtga aggtgctttg aaatcaagtg ctttgcaaa                289

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<210> SEQ ID NO 555

<211> LENGTH: 211

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 555

```
gaaaaaactt tctctttgcc atttcttctt cttctttttt aactgaaagc tgaatccttc    60
catttcttct gcacatctac ttgcttaaat tgtgggcaaa agagaaaaag aaggattgat    120
cagagcattg tgcaatacag ttccattaac tcttccctc gctccccc aaatttgaat    180
tttttttca acactcttac acctgttatg g                                211
```

<210> SEQ ID NO 556

<211> LENGTH: 130

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 556

```
tcttttttca gaatctatta aggacacttg aaagttttga aatttttggg aaatttggac    60
taccatgagg aaacttttga gattcaagtt cattctattc agagcaattc cgatattgat    120
gttaacttga                                130
```

<210> SEQ ID NO 557

<211> LENGTH: 233

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 557

```
caattttgtg cctaaattgc acattagaag atggattgat tggacacatc catgtaattc    60
aaagttatta ttcaaatattg acttaattgg taatcattga aaaaactgac taatgtcatt    120
tagtgtgaag gagcactggc cagctatatg ccacactcat acatatgcac tttcagaatg    180
tgagcagctt tctgaattt ttaatcaaac cttttcacca actttactga atg          233
```

<210> SEQ ID NO 558

<211> LENGTH: 152

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 558

```
gtaaatcact gtaaacgtgt cttcatttac tctagccaaa aggcctgggt tctgatagga    60
aactggtaag aaactcttca tgaaaacaca tcactaatat tcgctattac tctcctgggc    120
tgaagtcagc ttttctgaac cattaaggta tt                                152
```

<210> SEQ ID NO 559

<211> LENGTH: 175

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 559

```
gagttgtatc gtgtggtgta ttttttaaaa aatttgattt agcattcata ttttcattt    60
tattcccaat taaaagtatg cagattattt gcccaaagtt gtcctttttt tcagattcag    120
catttgtttt ttgccagttt cattttcatt tttttccatg gttccacaga agctt        175
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<210> SEQ ID NO 560

<211> LENGTH: 226

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 560

taaagggtggt ttggcctcta atttaatttt gattcagact ctctgtcag gactcaagaa 60

aatttaatta attaccaagg attaagtttt ttggttaagg tttttgggaa aaaaaaatag 120

caaagatggt gatttcttgg aatcctttta caggttcata acagaaaaat cttcattccc 180

tgtaggcatt taattaaacc tagttgagaa gtgtgtggga ttcttc 226

<210> SEQ ID NO 561

<211> LENGTH: 270

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 561

ctgttccttt cctgggttcc aattttgtgc cttaaattgca cattagaaga tggattgatt 60

ggacacatcc atgtaattca aagttattat tcaaatttga cttaattggt aatcattgaa 120

aaaactgact aatgtcattt agtgtgaagg agcactggcc agctatatgc cacactcata 180

catatgcatt ttcagaatgt gacgagcttt tctgaatttt taatcaaacc ttttcaccaa 240

ctttactgaa tgctactgg aattccataa 270

<210> SEQ ID NO 562

<211> LENGTH: 215

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 562

caaggccctg ctgtaagtat gatttgggga aataataaag aagatcacgg acctaggaat 60

gttttcttca gactaaacca agacaacttt gacaacccat taagttagcc ccatttcaat 120

atatactcta aaatatctgg aaattgtcta aatgcaatgg gctgtaagtc catccctgca 180

gtgggcctgg gggctcgta tttatttatg gtgaa 215

<210> SEQ ID NO 563

<211> LENGTH: 181

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 563

gagttgtatc gtgtggtgta ttttttaaaa aatttgattt agcattcata ttttccatct 60

tattcccaat taaaagtatg cagattattt gcccaaatct tcttcagatt cagcatttgt 120

tctttgccag tctcattttc atcttcttcc atggttccac agaagctttg tttcttgggc 180

a 181

<210> SEQ ID NO 564

<211> LENGTH: 225

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 564

ttttctgcac atttacttgc ttaaattgtg ggcaaaagag aaaaagaagg attgatcaga 60

gcattgtgca atacagtttc attaactcct tccctcgtc ccccaaaaat ttgaattttt 120

-continued

ttttcaacac tcttacacct gttatggaaa atgtcaacct ttgtaagaaa accaaaaataa 180

aaattgaaaa ataaaaacca taaacatttg ccaactttct tgtac 225

<210> SEQ ID NO 565

<211> LENGTH: 211

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 565

gaaaaaactt tctctttgcc atttcttctt cttctttttt aactgaaagc tgaatccttc 60

catttcttct gcacatctac ttgcttaaat tgtgggcaaa agagaaaaag aaggattgat 120

cagagcattg tgcaatacag ttccattaac tccttcccc gctccccaa aaatttgaat 180

ttttttttca acactcttac acctgttatg g 211

<210> SEQ ID NO 566

<211> LENGTH: 68

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 566

ctggaaaaga tggctgcact ggacatcctg gtacagttgg acctgctggc attcgaggcc 60

ctcagggt 68

<210> SEQ ID NO 567

<211> LENGTH: 83

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 567

taataacatg gcacagtgaa tgcttcttta gagtaaaaag gttttcttta acttgtaag 60

tcagagttgt ctaagtaatt gta 83

<210> SEQ ID NO 568

<211> LENGTH: 275

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 568

gttatggtgc taatgtactt tcacttttaa actctagatc agaattgttg acttgcatc 60

agaacataaa tgcacaaaat ctgtacatgt ctcccatcag aaagattcat tggcatgcca 120

caggggattt tcctccttca tcctgtaaag gtcaacaata aaaaccaaata tatggggctg 180

cttttgtcac actagcatag agaatgtgtt gaaatttaac tttgtaagct tgtatgtggt 240

tgttgatctt ttttttcctt acagacaccc ataata 275

<210> SEQ ID NO 569

<211> LENGTH: 65

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 569

ttaactccat atgtgttctt cttgttttaa ttttgtcaac cagtgaagt gaccgacaaa 60

attcc 65

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<210> SEQ ID NO 570
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 570

taaagacgca tgttatgggtg ctaatgtact ttcactttta aactctagat cagaattggt      60
gacttgcatc cagaacataa atgcacaaaa tctgtacatg tctcccatca gaaagattca      120
ttggcatgcc acaggggatt ctctctcttc atcctgtaaa ggtaacaat aaaacacaaa      180
ttatggggct gcttttgtca cactagcata gagaatgtgt tgaaatttaa ctttgtaagc      240
ttgtatgtgg ttgtgatct ttttttctct tacagacacc cataat                      286

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<210> SEQ ID NO 571
<211> LENGTH: 111
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 571

aattgatggc tcttgatttg cagctgtatc tggagcttac cgaatctagt gcagctttaa      60
aaataggagg ccgattctgt ttccaagttc agaaggagca gcgatttggc a              111

```

```

<210> SEQ ID NO 572
<211> LENGTH: 261
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 572

agccgctgcc aagtctgtat gagaagaaca taatgaagcc tgactcagct aatgtcacia      60
catggtgcta cttcttcttc tttttgttaa cagcaacgaa ccctagaaat atatcctgtg      120
tacctcactg tccaatatga aaaccgtaaa gtgccttata ggaatttgcg taactaacac      180
accctgcttc attgacctct acttgctgaa ggagaaaaag acagcgataa gctttcaata      240
gtggcatacc aaatggcact t                                              261

```

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<210> SEQ ID NO 573
<211> LENGTH: 257
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 573

tcagcagggc atcgcatgga ccgcaggagg gcagattcgg accactaggc ctgaaatgac      60
atttcactaa aagtctccaa aacatttcta agactactaa ggccttttat gtaatttctt      120
taaatgtgta tttcttaaga attcaaattt gtaataaaac tatttgata aaaattaagc      180
ttttattaat ttgttgctag tattgccaca gacgcattaa aagaaactta ctgcacaagc      240
tgctaataaa tttgtaa                                                  257

```

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<210> SEQ ID NO 574
<211> LENGTH: 139
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 574

gaaaaagaaa tacaccccat ttctgggtgcc agtcagtgtc tgtctgtctc tgtatacata      60
cttatgtata aatatgtgtt tgtatatatg tttatataca tatatatttg ttcattgtat      120

```

-continued

tttggtttga cacttttaa 139

<210> SEQ ID NO 575
<211> LENGTH: 226
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 575

tcaactgccaa ttccagcacg aagttgggcg actgccaggc aggcactccc agtcgtcaaa 60
aagtgc aaat gttactcagg gaacaattaa tgtgagttgt gtaatgtaat atgggtcaaa 120
aacatgaaaa gacgttttaa atgtcagcgg atggctcagc ccacccatca gccagccaga 180
gagcagaaca cctgttttgc actcagtggc acagaagcca caattt 226

<210> SEQ ID NO 576
<211> LENGTH: 263
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 576

tcaggcccg agaccgggtg ttcctccaga tgccctcaga acaggctgca ggactgtatg 60
ccgggcagta tgtccactcc tcttttccag gatatttatt gtatcccatg taaaaacaaa 120
aaaacaaaaa acaagaaaaa gaaagagatt ttatagaaga aaatgacaca caaaaaatc 180
caaatgaaaa acataattgc ttcaaacac ttacacagtt ggaaagtat atgtaagtga 240
aaatttgac cattgtgtac aaa 263

<210> SEQ ID NO 577
<211> LENGTH: 245
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 577

attgtgctat aatccctatt tagttcaaaa ttaaccagaa tttttccatg tgaaatggac 60
caaaactcata ttattgttat gtaaatacag agttttaatg cagtatgaca tcccacaggg 120
gaaaagaatg tctgtagtgg gtgactgtta tcaaatattt tatagaatac aatgaacggt 180
gaacagactg gtaacttggt tgagttocca tgacagattt gagacttgtc aatagcaaat 240
cattt 245

<210> SEQ ID NO 578
<211> LENGTH: 212
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (125)..(125)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 578

acaggccaga ttatacaata cttctgtgca caccagatgg ttgtaaagaa agatcagcga 60
gaaaggcttt ggaagtttta atccttcttt ccaccttttt tccccgcatt ttagtaaatc 120
acaancctac ctgactggca tccaattatc agagatatcc agtgtttaag ctaccctctt 180
taaaagaaaa tgatctcttc ttattcctaa gg 212

-continued

<210> SEQ ID NO 579
<211> LENGTH: 221
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 579

taatgtcatc ctgtactcgg cacaaatcaa aggccaatac aagtctgaaa agcagaaata	60
aatatttttc cagggttttg ctcgggcaca tactaaactgc tttgggcatt ttaatctggt	120
ctccaaacac caaagaccca ttctgagcct gctattagcc tgctgctgac tctatcactt	180
ggagcaataa tgtgggggta tgggtggtga atcttgtata t	221

<210> SEQ ID NO 580
<211> LENGTH: 224
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 580

taccaccccc taaatcattc cagtgtcttc aaaaagcatg tttttcaaga tcattttgtt	60
tgttgctctc tctagtgtct tcttctctcg tcagtcttag cctgtgccct ccccttacct	120
aggcttaggc ttaattacct gaaagattcc aggaaactgt agcttcctag ctagtgtcat	180
ttaaccttaa atgcaatcag gaaagtagca aacagaagtc aata	224

<210> SEQ ID NO 581
<211> LENGTH: 174
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 581

gatagttgta caataatgtc tgagtactta atgccactaa actgtacact taaatgtcta	60
aaatggtaaa attttatgta tattttacct caattaaaaa gaaaacacct tggcccccaa	120
aggtaacttt gccaaagaac caaggctgaa atttcttgct aaatgagata attta	174

<210> SEQ ID NO 582
<211> LENGTH: 189
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 582

gatagttgta caataatgtc tgagtactta atgccactaa actgtacact taaatgtcta	60
aaatggtaaa attttatgta tattttacct caattaaaaa gaaaacacct tggcccccaa	120
aggtaacttt gccaaagaac caaggctgaa atttcttgct aaatgagata attaaatgct	180
tttcattgc	189

<210> SEQ ID NO 583
<211> LENGTH: 181
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 583

atctcaagat gaacagggtgc acctactttt gctccctctt tttttttttt ttctcttatg	60
tgtggaccca cataatcag ttectcaaac atttgctgag cacctacttg aggaggcagt	120
attagggtca tggttaagag ccagggccct gggttcacat cccagggtag ctgtgacctt	180
g	181

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<210> SEQ ID NO 584

<211> LENGTH: 145

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 584

caataaaagt ggcagacctc ttatccctg ttccacaaat aaatggaggc acagaatggg 60

gaagtggagg ccgagggaac aaagccaatt aagactgccg gcccggttcc ctggccacag 120

cactgagggt ttgaggggtg cctcc 145

<210> SEQ ID NO 585

<211> LENGTH: 249

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 585

aaagtagaac ctatggaatc cattcaaat ctgtactgag cattgattgt atgcactcc 60

tgtgtctagg ccttttgcac atgcactcac tcattcaaca gactttgacc ctgcctgctc 120

ttctgccagg ccgtgtgcta agggcctgcg atcccaagat aaatccctgt ctccaagcca 180

agcatgtgac tttgaagcag tgtaacttgg tgaggaacgt cttattttat ctctttacca 240

catcaacag 249

<210> SEQ ID NO 586

<211> LENGTH: 222

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 586

gtcccagggc ggtagtgaat acgcagcagc ggatcagatc agctttcagg gccccgacac 60

cccctgagca cctactgctt tgccctttta actggcacia gggttcagtt tacaggccaa 120

gggtatcaag ctgacttcc tggttccatt ttcattgtat ttttagcatt gccttctgtg 180

tatgacaaat tttactgctt tgggtgttat atggtgacat aa 222

<210> SEQ ID NO 587

<211> LENGTH: 293

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 587

gagccttcag gccagctggg tttagccga ggctgggttt agatgcagcg actgtttcag 60

gggtgactca gaagaaaaag aagctgagga agctgttggg gggctgaggg tgggattctc 120

gctccttcac ttcaggttac tcgtttctca gcaagttggc aaaacagaca tcatgctggt 180

gagtgccacg ttactccctt ggctggaaat gcttttctga aagtatgagt gttgtgccta 240

cttaattctg ataaacctgt ttaagcaata cttaggaggc ttacttcttt gga 293

<210> SEQ ID NO 588

<211> LENGTH: 168

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 588

gatacactat acaatcctat gaccaatctc atctacaact ttattcaaat tttatagagg 60

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ctgaggtgga aggatcactt gagtttgaaa ccagcctggg caacatagtg agaccccgtc 120

tctacaaaaa gtaggaaaaa aaaaatagcg aggtgttggtg gtacacgc 168

<210> SEQ ID NO 589

<211> LENGTH: 118

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 589

agggatatgaa ggttctctct gtgtcatttc ttaaaactcc atgtgagtct atagtgagtt 60

ttaaaaagaa aaagttccag cctgggcagc atagcgagac ctattgtctc tacacata 118

<210> SEQ ID NO 590

<211> LENGTH: 238

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 590

atgctctaaa acagtgtagg atttaagaat agatgggttt taatcctgga aattgtgatt 60

gtgacccatg agtggaggaa ctttcagttc taaagctgat aaagtgtgta gccagaagag 120

tacttttttt tttgtaacca ctgtcttgat ggcaaaataa ttatggtaaa aaacaagtct 180

cgtgttttatt attccttaag aactctgtgt tatattacca tggaacgcct aataaagc 238

<210> SEQ ID NO 591

<211> LENGTH: 257

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 591

caggctgttt gggcattaat tttgcttttt gagccttaag tgtgttagta ggatggagaa 60

actgtgatgg gggactggga acctggattg tctgatttta ggtcactgtt ccttgggcct 120

gtttttgtga gcccttacac aggaagatat aaagagagtt ctttcatttc cctgctaaaa 180

tcagtatgta gtatggggaa tgtatttggg ttgtttttta agaaaagggg aacagaatca 240

ggagagtggg caaaggc 257

<210> SEQ ID NO 592

<211> LENGTH: 238

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 592

tctttcatcg ccttcctca aaaaaacctg ctccgttgaa gtaactaag taactcaata 60

ttctttattt tggtttggaa cctgtctcaa ttttttgtat ccatattaag aagtcaccct 120

ataatctaaa ctttgaatt ctaatttttt tgtccatta tcatacaaag tgcttttaaa 180

cttgttttta aaaaatgaca gataatgcca catgaatagg aagatgattc attctaaa 238

<210> SEQ ID NO 593

<211> LENGTH: 219

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 593

tgttccacaa agaacgcaac acagtcttta aactttttgg tgtaagcttt tagccttggg 60

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tattttccag tggggaatgt ttaaaaaatat ttgaccaaac caaagacttt ttgcctttta	120
tagcaagcat aaagactgta ctgcctggct tttgtattcc ttcagacatt attgtaaag	180
tgcaactcct tttccctcct gtaaaccttt ataagatgt	219

<210> SEQ ID NO 594
 <211> LENGTH: 173
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 594

ttcaggatgt aggaggacat gtatagtatg tcaaaaactg caagcttttc ccaacttta	60
ccttaccagc atgttaatat ccagtttttt tatagtttaa aagttaaagt gcctcatatt	120
ttgaaaatat ccattaagga cccaggaatt agcatttcac ttgtttatac att	173

<210> SEQ ID NO 595
 <211> LENGTH: 299
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 595

acaagtcata tcaggatgca gttttagaag atatttttaa gaagaatgac catgatgggtg	60
atggcttcat ttttccaag gaatacaatg tataccaacc cgatgaacta tagcatattt	120
gtatttttac ttttttttt agctatttac tgtactttat gtataaaaca aagtcacttt	180
tttccaagtt gtatttgcta tttttccct atgagaagat attttgattt ccccaatata	240
ttgattttgg tataataaat gtgaggctgt ttgcaaaact taacttgcag gaatgggtca	299

<210> SEQ ID NO 596
 <211> LENGTH: 237
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 596

accctatgtc ctttatttac aaagctgtgc tcctattcat gagcatggaa tgtttttcca	60
tttgtttgtg acatttttta tttctttcag gggatatctg taattctcat tatatatatc	120
ttttgcttcc ttggttagct gtatttttag gtattttagt cttcttgtgg caattgtgaa	180
tgggattgca ttcttgattt ggctcttggc ttgaatgtta ttaacgccac atttttt	237

<210> SEQ ID NO 597
 <211> LENGTH: 36
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 597

cccactaagc aacttgtgac acccacctct gcccg	36
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<210> SEQ ID NO 598
 <211> LENGTH: 225
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (140)..(143)
 <223> OTHER INFORMATION: n is a, c, g, or t
 <220> FEATURE:
 <221> NAME/KEY: misc_feature

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<222> LOCATION: (145)..(147)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (149)..(149)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (151)..(151)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (153)..(157)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (159)..(165)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (167)..(168)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 598

aaaatgaaca gttaaggctc ttaaagatcc ttgacatggc tagcaacata atgattgtca 60
ctctacctgg ggcttccaag ctacttgag tagggacaaa atatcttggc tcacgtattt 120
aagagcctga atattccagn nnnngnnnana nnnnnnnann nnnnntnnat ttttaataaca 180
taacactggt gctcattttg taagtataag tggtatagca gtttc 225

<210> SEQ ID NO 599
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 599

ctgtcagata ccctgtttct ggagtcacat cagtgaggag ggatgtgggt aagaggagca 60
gagggcaggg gtgctgtgga catgtgggtg gagaaggag ggtggccagc actagtaaag 120
gaggaatagt gcttgctggc cacaaggaaa aggaggaggt gtctggggtg agggagttag 180
ggagagagaa gcaggcagat aagttggagc aggggttggc caaggccacc tctgcctcta 240
gtccccaagg cctctctctg cctgaaatgt tacacattaa acaggatt 288

<210> SEQ ID NO 600
<211> LENGTH: 197
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 600

tgggcctgaa taagggttat cgaatggtgg tgaatgaagg ttcagatggg ggacagtctg 60
tctatcacgt tcacttccat gttcttgag gtcggcaaat gcattggcct cctggttaag 120
cacgttttgg ggataatttt ctcttcttta ggcaatgatt aagttaggca atttcagta 180
tgtaaagtaa cacactt 197

<210> SEQ ID NO 601
<211> LENGTH: 133
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 601

gtcataaaga aagcaagatg tcttgcttta ttaagaaaac ttaaacagca ctttgaagt 60

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 taagtggggc ggattgccca agcgcaggag ttcgagacca gcctggacaa cattggagaa 120

gccccatctc aac 133

<210> SEQ ID NO 602

<211> LENGTH: 359

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (35)..(36)

<223> OTHER INFORMATION: n is a, c, g, or t

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (38)..(39)

<223> OTHER INFORMATION: n is a, c, g, or t

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (41)..(41)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 602

ctggtggcga cagcatcttt gggaagatca tccgnnanna nataccagcc aaaatcattt 60

ttgaggatga ccggtgcctt gctttccatg acatttcccc tcaagcacca acacattttc 120

tgggtgatacc caaгааacat atatcccaga tttctgtggc agaagatgat gatgaaagtc 180

ttcttggaaca cttaatgatt gttggcaaga aatgtgctgc tgatctgggc ctgaataagg 240

gttatcgaat ggtggtgaat gaaggttcag atggtggaca gtctgtctat caggttcac 300

tccatgttct tggaggtcgg caaatgcatt ggcctcctgg ttaagcacgt ttgggggat 359

<210> SEQ ID NO 603

<211> LENGTH: 161

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (44)..(45)

<223> OTHER INFORMATION: n is a, c, g, or t

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (47)..(48)

<223> OTHER INFORMATION: n is a, c, g, or t

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (50)..(50)

<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 603

tcgctcggcc tgggtggcgac acgatctttg ggaagatcat ccgnnannan ataccagcca 60

aaatcatttt tgaggatgac cggtgccttg ctttccatga catttccctt caagcaccaa 120

cacattttct ggtgataccc aagaaacata tatcccagat t 161

<210> SEQ ID NO 604

<211> LENGTH: 206

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 604

ttctcccttc tacgtgtaca tcattaatcc ccattgccaa gggcattgtc cagaaactcc 60

cctgagacct tactccttcc agccccaaat catttacttt tctgtggtcc agccctactc 120

ctataagtca tgatctccaa agctttctgt cttccaactg cagtctccac agtcttcaga 180

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agacaaatgc tcaggtagtc actgtt 206

<210> SEQ ID NO 605

<211> LENGTH: 246

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 605

ttttccagcc ctatagccac cccaagagtg gttatgcctc ctcgattgct ccatactcta 60

acatctagct ggcttccctg tctattgcct ttctctgtat ctattttcct ctattttcta 120

tcattttatt atcaccatgc aatgcctttg gaataaaaca tacaggagtc tgtttttgct 180

atggaatgcc ccatggggca tctcttggtg acttattggt taagggttcc tcaaactgtg 240

atTTTT 246

<210> SEQ ID NO 606

<211> LENGTH: 93

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 606

ttcctgcct caactgagga cgtttacgac tgcaggggtg agcactgggg ctgggatgag 60

cctcttctca agcactggga gtttgatgct cca 93

<210> SEQ ID NO 607

<211> LENGTH: 177

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 607

tggaaggagt ggctgctctc caaactatgc caaggcggcg gcagagctgg tcttctggtc 60

tccttgagaa aaggttctgt tgccctgatt tatgaactct ataataagat atataggttt 120

tgtacctttt ttacaggaag gtgactttct gtaacaatgc gatgtatatt aaacttt 177

<210> SEQ ID NO 608

<211> LENGTH: 239

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 608

cttgtctcct ccccggtgct ccaatgtctt cagtgggggg cccctcttg ggteccctcc 60

tctgccatca cctgaagacc cccacgcaa acactgaatg tcacctgtgc ctgccgctc 120

ggteccacct gcggcccggtg ttgactcaa ctgagctcct ttaacgctaa tatttcgggc 180

aaaatcccat gcttgggttt tgtctttaac cttgtaacgc ttgcaatccc aataaagca 239

<210> SEQ ID NO 609

<211> LENGTH: 142

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 609

ggteccctgca gaagcgtggc attgtggaac aatgetgtac cagcatctgc tccctctacc 60

agctggagaa ctactgcaac tagacgcagc ccgcaggcag cccccaccc gccgcctcct 120

gcaccgagag agatggaata aa 142

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<210> SEQ ID NO 610

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 610

agcacactag cacacagcac acacacaaag acacagcaca cacatgcaca cacagcacac	60
acacgcgaac acagcacaca cgaacacagc acacacagca cacacacaaa cacagcacac	120
acatgcacac agcacatgca cacacagcac acacatgaac acagcacaca gcacacacat	180
gcacacagca cacacgcatg cacagcacac atgaacacag cacacacaaa cacacagcac	240
acacatgcac acacagcaca cacactcatg cgcagcacat acatgaacac agctca	296

<210> SEQ ID NO 611

<211> LENGTH: 238

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 611

agcagaattt cagccggcgc tgcgcgccag ggcgctccgc gctacctgcc cgcgcgcgcc	60
gcgctcgggt tcccggggag ggcgccagtg ctccgcgcgc gcccagcca aggtgaatcc	120
cgggcagcgc ctctctccgc ctgcccggga agcttgagct caacaattag ccttgatcc	180
tccgggggatt ccaatccacg gaacaacttc cctgctttcc ccgaactcgg acatttta	238

<210> SEQ ID NO 612

<211> LENGTH: 198

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 612

tgttttcccc aaatgtactg atcacactcc aggtctcccc aaaatctaga cagtgttttc	60
ttccatctct gaaggggtgtt aaaacctttc cctgaagcca cagtaattat gaaggttatt	120
ttttccccgg ctgctgccag cgtccaggcc actaacttat attcttaaga tgtgaaaatt	180
aatctcagct tcccctaa	198

<210> SEQ ID NO 613

<211> LENGTH: 209

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 613

aacaaccag actggctcct cactcccttt tccatcacta aaaatcacag agcagtcaga	60
gggaccagc aagaccaaag gaggggagga cagagcatga aaacccaaat ccatgcaaat	120
gaaatgtaat tggcacgacc ctacccccca aatcttacat ctcaattccc atcctaaaaa	180
gcactcatat tttatgcatc cccgcagct	209

<210> SEQ ID NO 614

<211> LENGTH: 150

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 614

agggaccag taagaccaa ggaggggagg acagagcatg aaaacccaaa tccatgcaaa	60
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tgaaatgtaa ttggcagcag cctcaccccc aaatcttaca tctcaattcc catcctaaaa 120

agcactcata ctttatgeat ccccgagct 150

<210> SEQ ID NO 615

<211> LENGTH: 295

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 615

ggcaagttct tccaatatga cacctggaag cagtcacccc agcgctgcg caggggctg 60

cctgcccctcc tgcgtgcccg ccgggggtcac gtgctcgcca aggagctcga ggcgttcagg 120

gaggccaaac gtcaccgtcc cctgattgct ctacccacccc aagaccccgc ccacgggggc 180

gccccccag agatggccag caatcggaag tgagcaaaac tgccgcaagt ctgcagcccg 240

gcgccacccat cctgcagcct cctcctgacc acggacgttt ccatcaggtt ccac 295

<210> SEQ ID NO 616

<211> LENGTH: 183

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 616

catcaggttc catcccgaaa atctctcggt tcacgtccc cctggggctt ctctgaccc 60

agtccccgtg ccccgctcc ccgaaacagg ctactctcct cggccccctc catcgggctg 120

aggaagcaca gcagcatctt caaacatgta caaaatcgat tggctttaaa cacccttcac 180

ata 183

<210> SEQ ID NO 617

<211> LENGTH: 170

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 617

tttgctttcc ccaaatgtac tgatcacact ccaggctccc ccaaaatcta gacagtgtt 60

tcttccatct ctgaaggggt ttaaaacctt tccctgaagc cacagtaatt atgaaggta 120

ttttttcccc ggctgctgcc agcgtccagg ccactaactt atattcttaa 170

<210> SEQ ID NO 618

<211> LENGTH: 262

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 618

tggtctgtat ggctctgagg ctccctgggg cctgctcaag ctctcctgc tcttctgtgt 60

tttctgatga tttgggggct tgggagtccc tttgtctca tctgagactg aaatgtgggg 120

atccaggatg gccttccttc ctcttaccct tctccctca gcctgcaacc tctatcctgg 180

aacctgtcct ccttttctcc ccaactatgc atctgttgtc tgctcctctg caaaggccag 240

ccagcttggg agcagcagag aa 262

<210> SEQ ID NO 619

<211> LENGTH: 165

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 619

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ctcagggagc gaacgtggat gaaaaccaca gggattccgg acgccagacc ccattttata    60
cttcactttt ctctacagtg ttgttttggt gttgttggtt tttatttttt atactttggc    120
cataccacag agctagattg cccaggtctg ggctgaataa aacaa                    165
```

<210> SEQ ID NO 620

<211> LENGTH: 191

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 620

```
ctttttaatg ttagtgatcc acctgcctca gcctcccaaa gtgctgggat tacaggcttg    60
aaagtctaac ttttttttac ttatatattt gatacatata attcttttgg ctttgaaact    120
tgcaactttg agaacaaaac agtcctttaa attttgcaact gctcaattct gtttttcgtt    180
tgcattgtct t                                                    191
```

<210> SEQ ID NO 621

<211> LENGTH: 220

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 621

```
gcctgtggcc acctctgggg cacaatgggg gctccccact gccagctctg cccctcgggt    60
tggggggagta tcccaggcct ctctgtggga cctgggcccc tgacgggcct ttccagcccc    120
ttttgaggac agacagtcoc ccgaggtagg ctacatcccc ccaccccagc tggctctgctt    180
ggatttccta cagcccccggt gggcatggac cacctttatt                    220
```

<210> SEQ ID NO 622

<211> LENGTH: 92

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 622

```
ggacagacag tcccccgagg taggtacat cccccaccc cagetggtct gcttggattt    60
cctacagccc ccgtgggcac ggaccacctt ta                                92
```

<210> SEQ ID NO 623

<211> LENGTH: 203

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 623

```
ggtaaaaatc caaattgtat cacagaaaat acagtgaata aaaccatcct cttaagaggg    60
tgtgtacatt tataaatttg cctatgattg cctataaagt caaagaagtt gcaccagtat    120
gcatgactgc caaaagtaca taaactgagc atatccattt ccctacattc ttgcaaacat    180
tgtgccttcg aacttttttg cct                                        203
```

<210> SEQ ID NO 624

<211> LENGTH: 294

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 624

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cagggttcct ttgcctgcta acaagccac gtggaccagt ttgaatgtct ttcctttaca	60
cctatgtttt taagtagtca aacttcaaga aacaatttaa acaagttttt gttgcatatg	120
tgtttgtgaa cttgtatttg tatttagtag gcttctatat tgcatttaac ttgtttttgt	180
aactcctgat ttttcctttt cggatactat tgatgaataa agaaattaaa gtgatagttt	240
tattggtttc ctttccccca attaaggcca aataaagtcg tgagaacatt acce	294

<210> SEQ ID NO 625
 <211> LENGTH: 106
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 625

atgtgtttgt gaacttgtat ttgtatttag taggttctta tattgcattt aacttgtttt	60
tgtaactcct gattcttctt tttcggatac tattgatgaa taaaga	106

<210> SEQ ID NO 626
 <211> LENGTH: 114
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 626

aggaggcaca gaccagtgtc tggatcccag catcttctcc acttcagcgc tgagtccagt	60
atacacaagt gtctgtctaca gtcgccaat caccagtatt tgcttatata gcaa	114

<210> SEQ ID NO 627
 <211> LENGTH: 195
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 627

actttctctc gccatgtagt gagtgaata taaacagtac ggcatgtggc acctgaacag	60
tcttcatgcc caggaatccc aaatgctgtt tactctacag aaaggaatca cttgattttc	120
cacttcagaa gccaacggct caacaacact ggggaagaaa tgaagaatcc tgggtctcct	180
tgtagtcgat caaga	195

<210> SEQ ID NO 628
 <211> LENGTH: 172
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 628

agcccaccca ttgaagtctc cttgggccac caaagggtgt ggccatggta ccggggactt	60
gggagagtga gaccagtgg agggagcaag aggagagggg tgtcgggggg gtggggcacg	120
gggtagggga aatgggggtga acggtgctgg cagttcggct agatttctgt ct	172

<210> SEQ ID NO 629
 <211> LENGTH: 157
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 629

tatgaattcc attcaaactg ttcctttttg ttaacaaggg gcatggggag gggtaggggt	60
gggggggcag aggcgtctga cccaggaac ctgcaggcgg gggctgggtc ggtgcccttt	120

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aaggacaatt ttgacctgtg tcaacctttc cacaaag 157

<210> SEQ ID NO 630
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 630

tggggggggca gaggcgtctg accccaggaa cctgca 36

<210> SEQ ID NO 631
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 631

gctctgggat cccttttcag tataacgctt ttattttagt ttttagagag acgaggtctt 60

gctctgttgc ccaggctggg tgcagcgggtg cgatcttggg tcaactgcagc ctccaactcc 120

ttggctcaag ctgtcctctg gcctcagcct cctgagtagc tgggaccaca ggcgagtgtc 180

accatgctgg gcagtataaa gttttaaatg cataaaataa aatccacaag atgaccaagg 240

aaggcaatta tgttgaaata cagatcaaaa tattaataaa acacacatct tatgtctt 299

<210> SEQ ID NO 632
<211> LENGTH: 245
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 632

gatgtgcctt aaattatacc aaagattact aattattcct ctttgcccaa aatacttgca 60

tccaaggttc tagtctctgt tgctgtgctg gtcttttagcc ccactgtgg cactgatgtc 120

cctccttttt cacggagacc tatctgaggt acaggatggg gctggcacca gatgatgtcc 180

caccacagtc cctcacctcc ggccctccaca tgacagaacc aatttacct caacctgac 240

ctcac 245

<210> SEQ ID NO 633
<211> LENGTH: 252
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 633

gattcgagga ccattgtaggt cttttacgta gcccaaatcc ataaattagt ctcacttttt 60

gtattttatcg tttcatatta aacctctat atcaaatgtt catcatgatt ttgtatgatt 120

tttataacta ttttattcat tttattagat ttatttttaa attttttaat ggtaaatatt 180

taaactgtgg aaaccactga aggtgcttat taactgtttt ccagatttg tacaagtatt 240

ggatgattcc tt 252

<210> SEQ ID NO 634
<211> LENGTH: 247
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 634

atttatacta atggttcata tcctttattg ctcaatgatc taattaaagg gatcattgcc 60

-continued

acatttcacg tttatatttc tacaatttgt ttagaaaaca tctcctgacc atatcagtag	120
ctcgtgttat ctttttatca actgcttccc agagtccata aacaatagaa attttggatt	180
gaaaagttca gcataaggag tttgagtcag taaaggatgg gataaaggag tcgagatgat	240
tcaatga	247

<210> SEQ ID NO 635
 <211> LENGTH: 202
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 635

tttatttatt ggtctgaaag gcatttcaaa ggtattataa taatatattg gtgtaattta	60
attggtgcaa catgctttat ggctcctgtc aaaattgggt ttcactcatt tgattgggtt	120
gagcccagaa cagcctacag gggaaaaaca agctggataa ccacccaaag tgtttgtatt	180
ttcgttggaa actgattttt gt	202

<210> SEQ ID NO 636
 <211> LENGTH: 300
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 636

cttagtttac acatctgcc aaggggtaga attacacttc tttttacagg taaatgtcaa	60
ggcacaatca gttttcagga agtgcttcaa gacccaggt gaaatgaaaa tgctaagtac	120
cctctgaatg gccatgctg ttaccaggtg ctgcttcttc agatgatggg gagcactttt	180
cagggtgaaa ttcaggcgag ttttgcccag gcctgctgtc ttgagtacaa atgtgaatga	240
tcgactgact gcttggtgcc aaactggaaa tgttctgtag ggatttactg gcatggtatc	300

<210> SEQ ID NO 637
 <211> LENGTH: 167
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 637

ctgaacagga gttgggataa tggccatctt ttctttccta tcctttcttc cccctcact	60
gtgaaaaata acagtccacc ccaagtcata cactggaccc agtgccctgcg gggacaggac	120
tgtgggtttc ttggtcacac ctgtgttggg gctcaatgca gtgtaga	167

<210> SEQ ID NO 638
 <211> LENGTH: 271
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 638

gactgtgctc tcttaaaaat aagaaagagc ctcttcatct tcaaaaggac tacatctgaa	60
gtttcccccag aaggacaaat gtctacttag acctataaaa tttccaaaat aagagagtca	120
gagccagagg tggctttaa gttgacttct gttgagatct gaccacattt gatctcttgt	180
tttaattttc caactaactg aacttggaag aaaacccaaa ccaagtttta atctgatgcc	240
taatcagccc gtctccaacc atcagagaaa a	271

-continued

<210> SEQ ID NO 639

<211> LENGTH: 234

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 639

```
ctccacttcc ctcagatgat gaggagccag ggctaagggg gcagccttct ctcttcccag    60
tgatgcacat ccttcacatt ggctgctttg ttctggaata tggatatctc agcctggatg    120
ccgaggaagc tgctggatgc ttaatgggtgc tagaggctca agtgtgtttg aaaccaagag    180
ccagttgtcc cccatgcaga aagaaatcct gtgtgagcct ctggtatgag aaat          234
```

<210> SEQ ID NO 640

<211> LENGTH: 261

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 640

```
gggagaagat gacccgtgga acacttgctt ggcccactca gaatccacgg tgacctttcc    60
gcttgccaaa ataaccgaag gaaagaccgt tcaccagact tggctccttt aaacatttgc    120
tgttcaaaca tgtttttgaa tatacattct ataaaagatt atttgaaaga caaaattcat    180
agaaaatgga gcaaaactgt ataaactgat ttgtaactaa cactggacca ttggatcgat    240
attatatgct gtaaccatgt g                                261
```

<210> SEQ ID NO 641

<211> LENGTH: 92

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 641

```
ctcaaaaaag tggttttgac cagagaggcc cagatggagg ctgttcattc cctgcagtgt    60
cggcattgta aataaagcct gagcacttgc tg                                92
```

<210> SEQ ID NO 642

<211> LENGTH: 238

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 642

```
gagcaggagc ctctacacag cctctggctc ttaggtccca gtcagtgttg cccccctca    60
aagggggcagg accagccctt cctttcagtg tccataccag gggccttcca tgtgctgatg    120
ggatgatgta ctgtggtcag caggcttggg aagtgtgtgt gctgtagctt gagttgggct    180
ggggtcttgg taggacgtgt atctcagaag tccccaaagt tcaactgtga ggtctcta    238
```

<210> SEQ ID NO 643

<211> LENGTH: 128

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 643

```
gaccagacag tgctgttggg gactgtccct gacttcagtg ccacgcagac cgctgcctt    60
gtgaacctgc gcagcctggc ctgccagccc atcagcttct cgggcttcgg ggcagaggac    120
gatgacct                                128
```

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<210> SEQ ID NO 644

<211> LENGTH: 152

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 644

```
gccatttaag ttaatgccgg gcttggtaca cttttaagag tgaaaagggg caggacaaat    60
gcaaagctca atggggctct tgggcaatac ggataaacca gggctgtttt gagtaaatca    120
aatgaggata cacagtcact gtgagaacca gt                                152
```

<210> SEQ ID NO 645

<211> LENGTH: 270

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 645

```
taaactctct agggccaaaa cctggtatgg tcattgggaa atgagtgtctc agggagatgg    60
agcttagggg aggtgggtgc ttccctocta gatgtcagca tacactcttt cttcttttgt    120
cccaggctca aaacatcttt cctagagaaa acaaaaggga ctaaactaga aatataaaga    180
gccctataca tgacaggtga tcacgtactg aatgattttg aagtagtaca aacaataaaa    240
attctcatte cgcacatca tgcggtccat                                270
```

<210> SEQ ID NO 646

<211> LENGTH: 216

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 646

```
aatgtgact cgacagcctt ttgccattgg tggctccggc agcaccttta tctatggtta    60
tgtgatgca gcatataagc caggcatgtc tcccaggagg tgcaggcgct tcaccacaga    120
cgctattgct ctggccatga gccgggatgg ctcaagcggg ggtgtcattt acctggtcac    180
tattacagct gccggtgtgg accatcgagt catctt                                216
```

<210> SEQ ID NO 647

<211> LENGTH: 214

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 647

```
tatcgggtatc ttagaaaacta tctatattct aggccaggag cagtggctca tgctgtaat    60
cccaacattt tgggaggtca aggtgggcag atccctagag ccaggagtt tgagaccagc    120
ctgggcaaca tggcaaaacc ccgtctctac aaaaaattta gctggatggg gtgcacctgt    180
aatcccaact agtcagaagg ctgacggga ggat                                214
```

<210> SEQ ID NO 648

<211> LENGTH: 45

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 648

```
gaggtggaaa gatcatctga gccggggaga tcaaggctgt agtga                    45
```

<210> SEQ ID NO 649

<211> LENGTH: 242

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (199)..(199)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 649

gagatgaaac tatgggcccc agactntact gcagcagctg tgatttcctc catagttggc 60
ttctgggtca ggcactaggg aatattttct tgaagacttc ttccaaatac ctgtggtctt 120
tgtccactg cagccaccag cctgtgcagg tagcgggtct catattgggg aaggggcttc 180
ccatccaaca gcagctgtnc ccccggtggg ctggtacaga ttctgcaaca gggcagccac 240
tg 242

<210> SEQ ID NO 650
<211> LENGTH: 214
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 650

tatcgggtatc ttgaaaacta tctatattct aggccaggag cagtggctca tgcctgtaat 60
cccaacattt tgggaggtca aggtgggcag atccctagag ccaggagtt tgagaccagc 120
ctgggcaaca tggcaaaacc ccgtctctac aaaaaattta gctggatggg gtgcacctgt 180
aatcccaact agtcagaagg ctgacggga ggat 214

<210> SEQ ID NO 651
<211> LENGTH: 76
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 651

ggcattggct aatgtttta taaattttat ctctaaaaat tcaaaccaaa aaacccctg 60
tattcacacc tgtaat 76

<210> SEQ ID NO 652
<211> LENGTH: 224
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 652

tccacacctg attagaacat tcataagcca catttagaaa cagatttgct ttcagctgtc 60
acttgcacac atactgccta gttgtgaacc aatgtgaaa aaacctcctt catccattg 120
tgtatttgat acctgccgag ggccaagggt gtgtgttgac aacgccgtc ccagccggcc 180
ctggttgctg ccacgtcctg aacaagagcc gcttcggat ggct 224

<210> SEQ ID NO 653
<211> LENGTH: 222
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 653

gaatcaccag ttgatactc tctgtaatca gaacagtggg cagtgcctgg gtgaacgtgt 60

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ctagcagcca ctgtgcggga tcgctgtaac aggagtggaa tgtacatatt tatttacttt	120
tctaactgct ccaacagcca aatgcctttt ttatgaccat tgtattcagt tcattaccaa	180
agaaatgttt gcactttgta atgatgcctt tcagttcaaa ta	222

<210> SEQ ID NO 654
 <211> LENGTH: 279
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 654

tggccacggc gcttggaaac ctggttggtg ctggatgctc ttttgcgatt aggagatacc	60
aaaaaaaaagc gacagcctga agcagccaca aaatcctgtg ttagaagcag ctgtgggggt	120
cccagtgagg atgagcctcc cccatgcctc cagcagcctg accctcgtgc cctgtctcag	180
gcgttctcta gatcctttcc tctgtttccc tctctcgtg gcaaaagtat gatctaattg	240
aaacaagact gaaggatcaa taaacagcca tctgcccct	279

<210> SEQ ID NO 655
 <211> LENGTH: 106
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 655

atagccctaa atgtactctt gaacttttta ctggaacaat gtttgatact ttagtatgta	60
agctgtatatt atgtaatatt tagaacgaca tgtaataaaa caaagt	106

<210> SEQ ID NO 656
 <211> LENGTH: 125
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 656

attggaaaag aaaaggaagc caggcgtggt ggctcatgcc tgtggtccta gcactttggg	60
agtccaaggc aggagatca cgaggtcagg agatcgagac catcctggcc ggcagggtaa	120
aacc	125

<210> SEQ ID NO 657
 <211> LENGTH: 70
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 657

ggaagactaa gttagctaca aagaaaacta agtattatac caaaaaaact tatccgggcg	60
tggtgacagg	70

<210> SEQ ID NO 658
 <211> LENGTH: 129
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 658

agctttattg tactggatat ctgtatttac tgagtatacc tatatgggag tcccttatat	60
tactttggaa taacagtttt tcatatataa aaaatgttgt gaaacttact gggagtgtat	120
gtaatatgc	129

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<210> SEQ ID NO 659
<211> LENGTH: 121
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 659

atataccata ggctaaaact aaggctttca ctctagaatg caaagctgtt ttgcagctgt	60
tttcccttaa agatgtcctg ttgctttagt gatatttaga cccctctcag ttaagaaatg	120
c	121

<210> SEQ ID NO 660
<211> LENGTH: 265
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 660

agatcactgc atccgcctat acaatcttta ccaataaaga ctcgaggcac cgttcttgct	60
cccgtgagct gttgcaaata atcttgaatc tcgttagtgt gggtgggtggc tgtgatatcg	120
acaaattcca gaagcccttg ttgatgggc aattgactga ggatctcttg ggccctctg	180
cagtacgggc aggtgggctt gatgaacaca accaccttcc caggctggat ttgcagttc	240
acaaactctt gagccatgcc gatgg	265

<210> SEQ ID NO 661
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 661

ttatagtata atattgggac cccataccgt tagcccttgt atgtatacca acactgccaa	60
agtaaaacat taggtcaggc at	82

<210> SEQ ID NO 662
<211> LENGTH: 253
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 662

gtcctcaggt gacatttgggt tgtgaaaagt gatattttag ttctaactac ctaagtcagc	60
agcaaagttt aaacagtaca gatttaaaaa ttttttataa aggaatttaa ctcttggtta	120
ctatattata tttagcttta ttgtactgga tatctgtatt tactgagtat acctatatgg	180
gagtccttta tattactttg gaataacagt ttttcatata taaaaaatgt tgtgaaactt	240
actgggagtg tat	253

<210> SEQ ID NO 663
<211> LENGTH: 81
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 663

gtcctcaggt gacatttgggt tgtgaaaagt gatattttag ttctaactac ctaagtcagc	60
agcaaagttt aaacagtaca g	81

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<210> SEQ ID NO 664
<211> LENGTH: 237
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 664

cagttccagt aattattgct gctgttggtt ccagacaaaa tgaagagtta ccttgtacat    60
gccactatg tacctcagac agaggagct gtgttagtac aactgaaggg atccaacttg    120
caaaagaact aggagcgacc tatcttgaac tccacagcct tgatgacttt tacataggaa    180
agtattttgg aggagtgttg gagtatttta tgattcaagc cttaaatacag aagacaa    237

<210> SEQ ID NO 665
<211> LENGTH: 95
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 665

tgccaaagta aaacattagg tcaggcatgg tggctcaggc ctgtaatccc agcattttgg    60
gaggctgagg caagtggata acttgaggtc atgag                                95

<210> SEQ ID NO 666
<211> LENGTH: 182
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 666

catggtggct tcatattaag tagtaacaga agtttgaaca attggataaa ttgacttcc    60
aagacagcta aacttttcaa ctgcaatttt aaaaactaca ctacactgtt atagttaatc    120
tgacaaaaat gtcctcaaag agtactttat tttatttaaa gcactctgtt aattcaacct    180
tt                                                                182

<210> SEQ ID NO 667
<211> LENGTH: 208
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 667

gatgaaaata ggcttgccac tttctcttat tttaattcca tggtagtcaa tgaactggct    60
gccactttta tataactgaa aattcatttt gagaccaagc aggatcaagt ttgtagaata    120
aacactgggt tcctagccat cctctgaaaa cagtatgaaa catgaccaag tacataatgg    180
athtagtaat aaatattgtc gaattgct                                208

<210> SEQ ID NO 668
<211> LENGTH: 210
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 668

ttagggccca gtcgagaccc agatccactg aacatctgtg tctttatttt gctgcttgta    60
tttattgtag tcaaatgctt tacatcagaa tgatgaaaat aggcttgcca ctttctctta    120
ttttaattcc atggtagtca atgaactggc tgccacttta atataactga aaattcattt    180
tgagaccaag caggatcaag ttgtagaat                                210

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<210> SEQ ID NO 669
<211> LENGTH: 289
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 669

atattgtccg ggtggataag aaccaggatt ttgtaacagg gaggaacaa gtcaaaatc      60
agaaaaaaga gatttgtcaa tggaacaaga ggttgaagtg ctttgaagtt ggaggaagag      120
gtcacaggca aaaaagtaca ggcagccttt agaaaaccaa aaggacaaag gaacagattt      180
tccccgggag tctgcagaag gaaccagccc tgcctgcaca tggcttttagc ccagtgcacac      240
tgattttgga catttgacct tcagaactgc ttgctcataa acttgtctt      289

```

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<210> SEQ ID NO 670
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 670

atattgtccg ggtggataag aaccaggatt ttgtaacagg gaggaacaa gtcaaaatc      60
agaaaaaaga gatttgtcaa tggaacaaga ggttgaagtg ctttgaagtt ggaggaagag      120
gtcacaggca aaaaagtaca ggcagccttt agaaaaccaa aaggacaaag gaacagattt      180
tccccgggag tctgcagaag gaaccagccc tgcctgcaca tggcttttagc ccagtgcacac      240
tgattttgga catttgacct tcagaactgc ttgctcataa acttg      285

```

```

<210> SEQ ID NO 671
<211> LENGTH: 185
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 671

attcaaaactc aagtccttgg agtgtcaca aggactaaca acgtggctg ggacaaaacc      60
tacagcttct ttaaatgtg agggggccct atggagaaat ggcccagtgt gtttctcatg      120
gggtgtctcct ccacttcccc acagaatgca atgaactcct gattccccag gtcacctaca      180
ggata      185

```

```

<210> SEQ ID NO 672
<211> LENGTH: 65
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 672

aactcaagaa atggcatcga aaagcaagtc aaaaccgtga gatttcagaa ttacagccct      60
cctcc      65

```

```

<210> SEQ ID NO 673
<211> LENGTH: 262
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 673

atgacaaggc aggacatcca atgccttcga gctctgtggt ctggcctgtc tctccagatc      60
agatttagag tgaggtagca gatgacataa tattctcttt ggtgttcaat ccgaagaggc      120
caatgcttca gcacaatgtc ccttagccat cacccccagc ccgactcccc accaagcatc      180

```

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ctgcacccct ctgccacatc ttcattcttt tccattctgt cttttccccc ataccttctg 240

accccaggga tttctaatag ag 262

<210> SEQ ID NO 674

<211> LENGTH: 242

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 674

aggatagatg gcgtggcctt ccaaacatac aaacataatg atttgatgcc acaaagctcg 60

cttactcaga ccaaggagtg aaaaattgtc gtgcccactt tatgcccag catggagtat 120

gtggcctctt gtcacccccg tgttactgtg tagaatttct atggtgtcct aaagggggct 180

gcagcagggg tgtgacaacg gtgggattgt tggcgttgct tctttgacct tacaatatcc 240

tc 242

<210> SEQ ID NO 675

<211> LENGTH: 251

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 675

ctctttaccg cgagactgat cagaagaagc aaaaggggaa agggggctag aggtccactc 60

gcacctttta catcagacaa gaggaggact gtgccagaaa tctgtgcatg aaacaccatc 120

tgctcttcat gcaggggagg gtcaaccgtg tgaacgtgca gagattactc gagccttctt 180

tgccaaaaat atgcattctt cccagctgta aggggtgtgaa gccaaatatg tcttttagca 240

tgaaacaata a 251

<210> SEQ ID NO 676

<211> LENGTH: 277

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 676

tgttggccac tccatattcc aaaagtaggg gagggccagc accagcatcg gagcacagca 60

ccatcctcac ccccatccac aagcagacca aggcggactg ttcttggett cctaaaggct 120

tcctaaagac aatgaggtga attttgccac agctctgaag agatgctcgt ttgcactaca 180

gatattccct gctagggatc aacagtctac aacagtgagg cactgctaac tgtacaaagg 240

cagttccatt cagtaccta gatccattct gggccca 277

<210> SEQ ID NO 677

<211> LENGTH: 269

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 677

agctgaacta gaactatgag ggggtggggg gagggcttgg aattatgggc tatttttact 60

gggggcaagg gagggagatg acagcctggg tcacagtgcc tgttttcaaa tagtccctct 120

gtcccaaga tcccagccag gaaggtggg gccctactgt ttgtcccctc tgggctgggg 180

tggggggagg gaggaggttc cgtcagcagc tggcagtagc cctcctctct ggetgcccc 240

ctggccacat ctctggcctg ctagattaa 269

-continued

<210> SEQ ID NO 678

<211> LENGTH: 171

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 678

agcttgttgc caaagtctgt tgagcagcac tgttgccaag ggtcctgggtg aagtcacccc 60

aggaggaaac cacagtctgt attccttgaa gggctgctgc acattgttga atccatcgac 120

ctttaactgc aatgggatct ctaatacatt ttgaggtcag ccacttctcc a 171

<210> SEQ ID NO 679

<211> LENGTH: 246

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 679

gaagctattg tccacagatt gatgcttcca taatggaatc agctttaatt gcaaggaatg 60

aagaaaaaca agagtggacc ttcaaagcta caacattttc ctctctccct cctctcccac 120

cagccccctc cccaccaaga actgttatga tgtcccaaag tgagggtgggtg ttgattccag 180

tctcaatggg attttctgac tttaatgttt gcaaggcatt tcaccagaat acagctataa 240

acggcc 246

<210> SEQ ID NO 680

<211> LENGTH: 276

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 680

taccatgttt ggtctaaatg tgcttaaaag ttttccaata actgaaatga gtatcagttt 60

taaatttaaa aatttgttac ttggttactc catatttcag gtattagtgg ctaccatatt 120

ggtcagagca gattcatagg atgatttccc aggtttgaag tgtgtgtata tttctgggat 180

tataagatgt cagactgggt ttgggagaaa tatgttgtct taatttttac ctgctttgat 240

atgacctttc tgtgtgtacg tgtgacattt ctttat 276

<210> SEQ ID NO 681

<211> LENGTH: 285

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 681

ccttctgttt gtgtacaaga gtaatttaaa agaaaaagct atgtgaaaat agttgggggtt 60

ttttgtgtgt tttgtttttt gtgggtgtga aggaggaggg ctaatgtcca gaggactgtt 120

tatccctgaa gtatgatata ctaaaatatt ttttattatt tgtatcaatt ttccttgag 180

ctcaatgtgc ccttgaggtt ttcagacttt attttaggaa aatatatttg catgttttcc 240

ccccatttcc aatgtttgggt gtctgtgttc atcatacccc acaga 285

<210> SEQ ID NO 682

<211> LENGTH: 211

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 682

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gaggcctgag gaaggtagta cttccacaaa agggaggagac cggggcccca gectcaagct 60
agtgggggag gcagatagcc tgaatccagg ggattttttg ggctttttaa aatgtccatt 120
gtgagttccc tgtgtttggg attccactca ttttggcatt cacagtgcct ggaatgtttt 180
agattttcag caatgcgtgt tgaataaatg a 211

<210> SEQ ID NO 683
<211> LENGTH: 98
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 683

catccagaaa aaggcagact aagaatcaga agccatgtga ttgatgtctg acgtgagtct 60
gtctcaggta gattccgggt gtcagtgtgg tttataat 98

<210> SEQ ID NO 684
<211> LENGTH: 62
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 684

tggaccaatg atgacaactg ccggcgtatg agtgttgggt gatgaataat acgtgtctag 60
aa 62

<210> SEQ ID NO 685
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 685

ggcgtatgag tcatacatga tgaatatgtg tctggaactc t 41

<210> SEQ ID NO 686
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 686

atgacaactg ccggcgtatg agtgttgggt gatg 34

<210> SEQ ID NO 687
<211> LENGTH: 250
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 687

atctagcatg cagagtgtag tgtgttgaaa cgggtgtatga cattgctgta tcaaagttgt 60
aaaattaagc attatttatt gaaaactatg tatttttttg taaaaacctg atcacataga 120
gaatatcagt ggcttgtgct tgtgcttcga tctaaccagc ttcttgaccc accccccctt 180
ggtatgcagt gttaatgctc aggggtgaaa atagtacact ccaatgtctc ttttgcaaga 240
gtttttcaca 250

<210> SEQ ID NO 688
<211> LENGTH: 259
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 688

gcgaggacgc cgacgacctg atgttcgacc tgagcttgaa tttctctcaa agcgcgcaca	60
gcgccagcga gcagcagctg gggggcgccg cggcgccggg gaacctgtcc ctgtcgtcgg	120
tggataagga tttggattcg ttcagcgagg gcagcctggg ctcccacttc gagttccccg	180
actactgcac gccggagctg agcgagatga tcgccccggg ctggtctggg gcgaacttct	240
ccgacctggg gttcacata	259

<210> SEQ ID NO 689

<211> LENGTH: 228

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 689

tgttgaaacg gtgtatgaca ttgctgtatc aaagttgtaa aattaagcat tatttattga	60
aaactatgta tttttttgta aaaacctgat cacatagaga atatcagtgg cttgtgcttg	120
tgcttcgac taaccagctt cttgaccac ccccccttgg tatgcagtgt taatgctcag	180
ggttgaaaat agtacctcc aatgtctctt ttgcaagagt ttttcaca	228

<210> SEQ ID NO 690

<211> LENGTH: 247

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 690

gcacggactg tcagtctctt gggaagtggg cagcgcatcc tgcagggtt ctcctctct	60
gtcttttggg gaaccagggc tcttctcagg ggctctaggg actgccaggc tgtttcagcc	120
aggaaggcca aaatcaagag tgagatgtag aaagttgtaa aatagaaaaa gtggagtgg	180
tgaatcggtt gttctttctt cacatttggg tgattgtcat aagggtttta gcatgttctt	240
ccttttc	247

<210> SEQ ID NO 691

<211> LENGTH: 95

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 691

ctattggaca gtgtctcttct agatcatcat aagactacag agcacttttc aaagctcatg	60
catgttcacg atgttagtgt cgtattttga gctgg	95

<210> SEQ ID NO 692

<211> LENGTH: 114

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 692

tcatcccat ggagcattgc accaccgct ttttcgagac ctgtgacctg gacaatgaca	60
agtacatcgc cctggatgag tgggcgggct gcttcggcat caagcagaag gata	114

<210> SEQ ID NO 693

<211> LENGTH: 170

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 693

```
acacaaattt cagcaccatt ctgcctgaaa tggcaccatc acaacctcag tcttgggtta    60
gggtgtgttc ctgtcctgag ttctctggga tggtaaaccac aggcagtagc ccttagttta    120
tctagatctg aaaaccaga catcagatat cgtcaaccaa gacatgggtg                170
```

<210> SEQ ID NO 694

<211> LENGTH: 131

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 694

```
ggtcagaagt agaattcttt catcatcaca gaaagttcta ttggacagtg ctcttctaga    60
tcatcataag actacagagc acttttcaaa gtcctatgat gttcatcatg ttagtgctgt    120
atcttgagct g                                                            131
```

<210> SEQ ID NO 695

<211> LENGTH: 153

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 695

```
atgggatggt cggatctcac aggcctgagaa ctggttcacc tccaagcatt tcatgaaaaa    60
gctgcttctt attaatacata caaactctca ccatgatgtg aagagtttca caaatctttc    120
aaaataaaaa gtaatgactt agaaactgcc caa                                153
```

<210> SEQ ID NO 696

<211> LENGTH: 222

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 696

```
tgttttcctc taattctect cactcccaaa caccaccttc cgtccccca atacacaaat    60
ttcagcacca ttctgctga aatggcacca tcacaacctc agtcttgggt taggtgttgt    120
tctgtctctg agttccttgg gatggtaaac acaggcagta gcccttagtt tatctagatc    180
tgaaaaccca gacatcagat atcgtcaacc aagacatggg tg                        222
```

<210> SEQ ID NO 697

<211> LENGTH: 175

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 697

```
aaaattagca tgctgctttt tgtacttga agtgtttcaa aaaattatat gaccatattt    60
actctttcta actttcttta ctccatcatg gctggttgat tttgtagaga aattagaacc    120
cataaccata cacaggctat caacatgtta ttcaatgtga cacctaactc ttttc        175
```

<210> SEQ ID NO 698

<211> LENGTH: 194

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 698

```
ttccaagctc ctgctgataa tgcagacttc ctggagtaca aacacaggat ttgtaattcc    60
```

-continued

ttactgtaac ggagtttaga gccagggtg atgctttggt gtggccagca ctctgaaact	120
gagaaatgtt cagaatgtac ggaaagatga tcagctatct tcaacataac tgaaggcata	180
tgctggccca taaa	194

<210> SEQ ID NO 699
 <211> LENGTH: 166
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 699

tgagtttccc tagagctgtg cgccagata gctgttcctg agttgcaagc acgatggaga	60
tttgacact gtgtgctttt ggtggggtgg agaggtgggg tggggtgggg tgtggtgggg	120
tggaggctgt ctgtgtccag gaaacttaat tccctggtga ctagag	166

<210> SEQ ID NO 700
 <211> LENGTH: 225
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (119)..(119)
 <223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 700

ctgtttcctt ctactgatgg ctagttaggt tattggaagt cttttgctgt tgctagttag	60
tcttgtatag acattgtaat gcacatgtgc aaaaatacaa gtatgatata atcttaaang	120
ggagttgctg agtccaatat atacattaca aatattgata gatattgcaa aattgccttc	180
atagaggcta tattaattta tagttccagc agcaacatat gagtt	225

<210> SEQ ID NO 701
 <211> LENGTH: 275
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 701

tccacctatc ccaaagtcgt atcaaagaag tggctgcaga ttggagccca aagcctttgg	60
ttcctcagtt tccaaatgga ttctcactag gtgggatcat gagtttgctt tggacacccc	120
aaattctaac tatttctttt gtttcttaca tcctttccct ctccccagc ccttccct	180
catgttacac ctcttgctgg ttgagacgt caatcaccac tgagaaagaa ttaaaccagt	240
atattgagct ggcaaaattc ttgacctagt acaat	275

<210> SEQ ID NO 702
 <211> LENGTH: 97
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 702

tccagctttg tgtttatctt tccagagaag ttactgtgt attaagcaaa tatgtatct	60
tttattcttg ctctgtatct tcgcaaacag cagctgt	97

<210> SEQ ID NO 703
 <211> LENGTH: 272
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 703

ttcccggagc agtgccctctg gatggactgg gtcacagaga agaacatcaa cgggcaccag	60
gccaaagtttt tcgcctgcat caagagaagt gacggctcct gtgcgtggta ccgcggcgcg	120
gcgcccccca agcaggagtt tttggacatc gaggacccat aagcaggcct ccaacgcccc	180
tgtggccaac tgcaaaaaaa gcctccaagg gtttcgactg gtccagcttt gacatccctt	240
cctggaaaaca gcatgaataa aacactcatc cc	272

<210> SEQ ID NO 704

<211> LENGTH: 151

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 704

tggacttgct gccgtaatth aaagctctgt tgattttgtt tccgtttgga tttttggggg	60
aggggagcac tgtgtttatg ctggaatatg aagctcgaga ccttcgggtg ctgggaacac	120
acaagagttg ttgaaagttg acaagcagac t	151

<210> SEQ ID NO 705

<211> LENGTH: 205

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 705

tgagctttga gtcaaatatg ggatgcagac caggtgtggt ggctcacgcc tgcatccca	60
gcactttggg aggccaaagg ggggtggattg tttgtgccca ggagttcgag actagcctgg	120
ccaacttcgc aaaacctgt ttttgcaaaa aataggcgtg gtggcatgta cctgtggtcc	180
cagctattca aaaggctgag atagg	205

<210> SEQ ID NO 706

<211> LENGTH: 162

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 706

tgtttttgac atcagctgta atcattcctg tgctgtgttt tttattaccc ttggtaggta	60
ttagacttgc ccttttttaa aaaaagggtt ttgcatcgta gaagcatttg acccagagt	120
gaacgcgtgg cctatgcagg tggattcctt caggtctttc ct	162

<210> SEQ ID NO 707

<211> LENGTH: 260

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 707

gagtaggttc ggtctgaaag gtgtggcctt tatatttgat ccacacacgt tggctcttta	60
accgtgctga gcagaaaaa aaacagggtta agaagagccg ggtggcagct gacagaggaa	120
gccgtctaaa taccttcaca ataaatagtg gcaatatata tatagtttaa gaaggctctc	180
catttggcat cgtttaattt atatgttatg ttctaagcac agctctcttc tctatttttc	240
atcctgcaag caactcaaaa	260

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<210> SEQ ID NO 708
<211> LENGTH: 84
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (53)..(53)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 708

tccctcaaag actgacagcc atcggtctgc acggggcttt ctgcatgtna cgncagctaa      60
gcataagtaag aagtccagcc tagg                                           84

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<210> SEQ ID NO 709
<211> LENGTH: 217
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (177)..(177)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 709

tgaaaacaag catgagtaga tcttgcttnc caatgggggc cttcccgctt gcttactgct      60
taggttttnc gcggtggggtc tgagcaatgc agaaagtttc ttacaatttc tctggattga      120
aacaagaaat agctccctcg ctccctcttca taaatttctc agagaaaatc taagtttcca      180
ggaagtagcc aaagaccagg agattgtgga atcaaaa                               217

```

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<210> SEQ ID NO 710
<211> LENGTH: 254
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 710

tgagcttccc ttggacacta actcttccca gatgatgaca atgaaattag tgctgtttt      60
cttgcaaatt tagcacttgg aacatttaaa gaaaggctca tgctgtcata tggggtttat      120
tgggaaactat cctcctggcc ccacccctgcc ccttcttttt gggttttgaca tcattcattt      180
ccacctggga atttctgggt ccattgccaga aagaatgagg aacctgtatt cctcttcttc      240
gtgataatat aatc                                                       254

```

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<210> SEQ ID NO 711
<211> LENGTH: 225
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 711

tagaggcttc ttagattctc ccagcatccg cctttccctt tagccagtct gctgtcctga      60
aaccagaag tgatggagag aaaccaacaa gagatctcga accctgtcta gaaggaatgt      120

```

-continued

atttggtgct aaatttcgta gcactgttta cagttttcct ccatgttatt tatgaatatt 180

atattccgtg aatgtatatt gtcttgtaat gttgcataat gttca 225

<210> SEQ ID NO 712

<211> LENGTH: 257

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 712

gaaagcctga gtttgcaacc agttgtaggg tttttgttgt gttttttttt tttttttgaa 60

ataaaactat aatataaatt ctccatttaa ataaaaattat tttaagtttt agtgtcaaaa 120

gtgagatgct gagagtaggt gataatgtat attttacaga gtgggggttg gcaggatggt 180

gacattgaac atgattgtct tctgtctctt ttttcagctt atgggtattt atcttctatt 240

agtatttgta tcttcag 257

<210> SEQ ID NO 713

<211> LENGTH: 267

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 713

tctgttaaaa tacagtgcag gccaggcgcg gtgactcagc cctgtaatcc cagcattttg 60

ggaggccaag ggtggcggat catgaggtca ggagatcgag accatcctgg ctaacacggt 120

gaaaccccat ctttactaaa aatacaaaaa attaaccagg tgtgggtggcg cacatctgaa 180

gtcccagcta cttgggaggc tgaggcagga taatcactta aacttgggag gtggagggtg 240

cagtgcagcg acacctcgcc actgcac 267

<210> SEQ ID NO 714

<211> LENGTH: 169

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 714

atccacagat atagccaagt agattgggta gaggatacta tttccagaat agtgtttagc 60

tcacctaggg ggatatgttg tatacacatt tgcataacc cacatggggg acataagcta 120

atctttttac aggacacaga attctgttca atgctgttaa atatgccaa 169

<210> SEQ ID NO 715

<211> LENGTH: 163

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 715

gatactttca ttttgcacat catgcacatc atggtattca ggggetagag tgattttttt 60

ccagattatc taaagttgga tgcccacact atgaagaaa tatttgtttt atttgcctta 120

tagatatgct caagggtact gggcttgcta ctatttgtaa ctc 163

<210> SEQ ID NO 716

<211> LENGTH: 216

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 716

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ccagctgttt gcgcgtttga cttttgtggc ctcagcagga caggccccgg gcaactgctc      60
acagccaagg ctggactggg ttggctgcag tgtggtgttt agtggatacc acatcggaag      120
tgatttttta aattggattt gaattcggtt cctgtttttt atttgcattg aaacagtgtg      180
tttggggaga tgctgtggga ggatgtaaat atcttg                                216

```

```

<210> SEQ ID NO 717
<211> LENGTH: 204
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

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<400> SEQUENCE: 717

```

```

aggaggagcg ccagttgccc ctgcctcaca gaccacacac ccagccctcc tgggccagcc      60
cagagggccc ttcagacccc agctgtctgc gcgtctgact cttgtggcct cagcaggaca      120
ggccccgggc actgcctcac agccaaggct ggactgggtt ggctgcagtg tgggttttag      180
tgataccac atcggaagtg attt                                204

```

```

<210> SEQ ID NO 718
<211> LENGTH: 219
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 718

```

```

ccagctgttt gcgcgtttga cttttgtggc ctcagcagga caggccccgg gcaactgctc      60
acagccaagg ctggactggg ttggctgcag tgtggtgttt agtggatacc acatcggaag      120
tgatttttta aattggattt gaattcggtt cctgtttttt atttgcattg aaacagtgtg      180
tttggggaga tgctgtggga ggatgtaaat atcttggtt                                219

```

```

<210> SEQ ID NO 719
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 719

```

```

caccactaaa agatcgagct ttgcctgggt cagtgg                                36

```

```

<210> SEQ ID NO 720
<211> LENGTH: 138
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 720

```

```

tcatgtttgc tgtagtctc atatttattg ttgtttttgt tttagtactc acttgtttca      60
taatatcaag attactaaaa atggggggaaa ggacttttaa tctttttttc ataatatctt      120
tgacacatat tacagaag                                138

```

```

<210> SEQ ID NO 721
<211> LENGTH: 283
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 721

```

```

gatcaagacc atagtgaacca acatagtga accccatctc tactgaaagt acaaaaaatta      60
gctgggtgtg ttggcacatg cctgtagtcc cagctacttg agaggctgag gcaagagaat      120

```

-continued

tgtttgaacc cgggaggcag aggttgacgt gtggtgagat catgccacta cactccagcc	180
tggcgacaga gcgagacttg gtttcaaaaa aaaaaaaaaa aaaaacttca gtaagtacgt	240
gttatttttt tcaataaaat tctattacag tatgtcaaaa aaa	283

<210> SEQ ID NO 722
 <211> LENGTH: 265
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 722

aacaaaatat ttctccccta gtgagagaaa gaggtcctca gagagtagca gctcacataa	60
ctgggaccag aggaagaagc aacacattgt cttctccaaa ctccaagaat gaaaaggctc	120
tgggcccga aataaactcc tgggaatcat caaggagtgg gcattcattc ctgagcaact	180
tgcacttgag gaatggtgaa ctgggtcatcc atgaaaaagg gttttactac atctattccc	240
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cagctacttg ggaggcctag gcgtgagaat cgcttgaacc tggaaggtagg tggttgcagt 240

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<212> TYPE: DNA

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<400> SEQUENCE: 728

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tcacctccga gagactgagt cacctttgac tcaagccagg tctttgaagg tagagccagg 180

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ctggggccta cctgaggctg gagcatggaa ggaggggtgag gatcaaaaaa ctacctatct      180
ggtactatgc tttttatctg gatgatgaaa taatctgtac aacaaacctt ggtgacatgc      240
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tggaggacca ggcactttga ggaagggcag ttcgtgggct ggggtgggaa caggatggcg      180
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<210> SEQ ID NO 734
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gtaacagggt tcgtgtgagt gtgcttgat acgtgagant tgccttattt tcaggttgtt      180
ttatttaacg atggttcctt ggacagcatt ctggtgttca gcaaccaata tggaat          236

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1. A method for selecting whether to administer an anti-angiogenic therapeutic agent to a subject, comprising:

measuring the expression level(s) of one or more biomarkers selected from Table 2 or Table 3 in a sample from the subject;

assessing from the expression level(s) of the one or more biomarkers whether the sample from the subject is positive or negative for a biomarker signature,

wherein if the sample is positive for the biomarker signature an anti-angiogenic therapeutic agent is contraindicated.

2-7. (canceled)

8. A method of treating cancer comprising administering a chemotherapeutic agent and not administering an anti-angiogenic therapeutic agent to a subject wherein the subject is selected for treatment with a chemotherapeutic agent by

measuring the expression level(s) of one or more biomarkers selected from Table 2 and Table 3 in a sample from the subject;

assessing from the expression levels of the biomarkers whether the sample from the subject is positive or negative for a biomarker signature,

wherein if the sample is positive for the biomarker signature the subject is selected for treatment.

9-12. (canceled)

13. The method of claim **8** wherein the chemotherapeutic agent comprises a platinum-based chemotherapeutic agent, an alkylating agent, an anti-metabolite, an anti-tumor antibiotic, a topoisomerase inhibitor, a mitotic inhibitor, or a combination thereof.

14. (canceled)

15. The method of claim **8**, wherein the chemotherapeutic agent comprises carboplatin and/or paclitaxel.

16. The method of claim **8**, wherein the anti-angiogenic therapeutic agent is a VEGF-pathway-targeted therapeutic agent, an angiopoietin-TIE2 pathway inhibitor, an endogenous angiogenic inhibitor, or an immunomodulatory agent.

17. The method of claim **16**, wherein the VEGF pathway-targeted therapeutic agent is selected from Bevacizumab (Avastin), Aflibercept (VEGF Trap), IMC-1121B (Ramucirumab), Imatinib (Gleevec), Sorafenib (Nexavar), Gefitinib (Iressa), Sunitinib (Sutent), Erlotinib, Tivozinib, Cediranib (Recentin), Pazopanib (Votrient), BIBF 1120 (Vargatef), Dovitinib, Semaxanib (Sugen), Axitinib (AG013736), Vandetanib (Zactima), Nilotinib (Tasigna), Dasatinib (Sprycel), Vatalanib, Motesanib, ABT-869, TKI-258, and a combination thereof.

18. The method of claim **16**, wherein the angiopoietin-TIE2 pathway inhibitor is selected from AMG-386, PF-4856884 CVX-060, CEP-11981, CE-245677, MEDI-3617, CVX-241, Trastuzumab (Herceptin), and a combination thereof.

19. The method of claim **16**, wherein the endogenous angiogenic inhibitor is selected from Thrombospondin, Endostatin, Tumstatin, Canstatin, Arrestin, Angiostatin, Vasostatin, Interferon alpha, and a combination thereof.

20. The method of claim **16**, wherein the immunomodulatory agent is selected from thalidomide and lenalidomide.

21. The method of claim **16**, wherein the VEGF pathway-targeted therapeutic agent is bevacizumab.

22. The method of claim **8**, wherein the biomarkers comprise one or more of IGF2, SOX11, INS, CXCL17, SLC5A1, TMEM45A, CXCR2P1, MFAP2, MATN3, or RTP4.

23. The method of claim **8**, wherein the biomarkers comprise the biomarkers listed in Table 2.

24-25. (canceled)

26. The method of claim **8** wherein the cancer is ovarian cancer, optionally high grade serous ovarian cancer, or colorectal cancer.

27-28. (canceled)

29. The method of claim **8**, wherein the biomarkers comprise one or more of IGF2, CDRI, COL3AI, SPARC, TIMP3, INS, COL8AI, NUAKE, MATN3, and TMEM45A.

30. The method of claim **8**, wherein the biomarkers comprise one or more of INS, SPARC, COLAI, COL3AI, CDRI, NUAKE, TIMP3, and MMP14.

31. A method for determining the clinical prognosis of a subject with cancer, comprising:

measuring the expression level(s) of one or more biomarkers selected from Table 2 or Table 3 in a sample from the subject;

assessing from the expression level(s) of the one or more biomarkers whether the sample from the subject is positive or negative for a biomarker signature,

wherein if the sample is positive for the biomarker signature the subject has a good prognosis.

32-45. (canceled)

46. A method for selecting whether to administer Bevacizumab to a subject, comprising:

in a test sample obtained from a subject suffering from ovarian cancer, which subject is being, has been and/or will be treated using a platinum-based chemotherapeutic agent and/or a mitotic inhibitor;

measuring expression levels of one, two or more, up to all of the, biomarkers selected from Table 2 or Table 3;

assessing from the expression level(s) of the one, two or more biomarkers whether the sample from the subject is positive or negative for a biomarker signature

selecting a treatment based on whether the sample is positive for the biomarker signature, wherein if the sample is positive for the biomarker signature Bevacizumab is contraindicated.

47-59. (canceled)

60. A method for determining clinical prognosis of a subject, comprising:

a. in a test sample obtained from a subject suffering from ovarian cancer or colorectal cancer, which subject is being, has been and/or will be treated using a platinum-based chemotherapeutic agent and/or a mitotic inhibitor;

b. measuring expression levels of one or more, up to all of the, biomarkers selected from Table 2 or Table 3;

c. assessing from the expression level(s) of the one or more biomarkers whether the sample from the subject is positive or negative for a biomarker signature, wherein if the sample is positive for the biomarker signature the subject has a good prognosis.

61-77. (canceled)

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